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PHYSIOLOGY OF THE COLON

LAWRENCE M. LARSON, M.D.
Fellow in Surgery, the Mayo Foundation

AND

J. ARNOLD BARGEN, M.D.
ROCHESTER, MINN.

The large intestine in most animals, including man, is generally regarded as possessing merely storage function similar to that of a catch basin so that defecation may take place at a convenient time. In other words, it is looked on as a fixed tube, or system of tubing, present mainly to transmit feces. Metchnikoff's claim that man at one time made use of his large intestine as a reservoir, enabling him to pursue his prey or run away from enemies without undergoing risk of stopping to evacuate the bowels, no doubt contains much truth. However, his belief that people can live without this portion of the intestine, and that of Lane,[1] Waugh[2] and others regarding intestinal stasis and other possible evils for which the colon can be responsible, have thrown this organ into disrepute and probably have discouraged extensive study of its physiology. It is true that individuals can live without the large intestine; that certainly is no proof of its uselessness. On the other hand, it is no doubt true that this organ is undergoing a process of evolution better to suit changing needs and fashions, a fact which especially emphasizes itself in a consideration of present-day dietary standards. Under the conditions of living in the twentieth century, it is true that in certain instances the colon can be removed and not be missed, yet that does not prove that it is of no significance in human economy. It also may be possible that the organ has outlived its usefulness in the process of development of the body, but there can be no doubt that in lower animals its functions are definite and its loss is attended with serious results. However, in man, although to less extent, possibly, it has been proved that the colon can be removed without injury.

1. Lane, W. A.: The Operative Treatment of Chronic Intestinal Stasis, ed. 4, London, Henry Frowde, 1918.

2. Waugh, G. E.: The Morbid Consequences of a Mobile Ascending Colon with a Record of 180 Operations, Brit. J. Surg. 7:343 (Jan.) 1920.

and there is no question as to the advisability of colectomy in such conditions as multiple diffuse polyposis.

From a study of the physiology of the large intestine it may be concluded that it is a bifunctional organ and, indeed, when one considers its embryologic development such a conclusion is obvious. Beginning low in the pelvis in the embryo and ascending upward in the median line, or slightly to the left, in the early months of fetal life the colon is a left-sided organ up to the splenic flexure, and it remains so in afterlife, held in place by peritoneal fusion. From the splenic flexure, it festoons itself across the abdomen to another fixed point under the liver, arriving there at about the third or fourth month, whence it extends to the right iliac fossa to a semifixed situation in adults. This rotation around the superior mesenteric vessels is counterclockwise and constant, except in a small number of variants. In addition, the left half of the colon is developed from the hindgut, whereas on the opposite side it takes its origin with the small bowel below the papilla of Vater from the midgut, or the absorptive portion of the gastro-intestinal tract. This embryologic difference and the development of the proximal portion of the colon with the small bowel early called attention to the fact that there must be dissimilarity of physiologic function in the two halves, and the normal association of the proximal portion of the colon with the small bowel from the standpoint of physiology was readily established. Anatomic differences in conformation and construction in the two halves likewise indicated a difference of purpose. When pathologic processes developed, a study of them indicated that different types of lesions were found as a routine in the two arms of the colon, producing different symptoms. For example, a malignant lesion of the right side of the colon clinically called attention to itself by disturbances of the physiologic equilibrium, in sharp contradistinction to the obstructive phenomena characteristic of the distal part of the colon.

The cecum has long been regarded as a second stomach of primary significance in digestion and absorption, especially regarding cellulose in the herbivora; likewise, its enormous variation in size and appearance in various animals has been a subject of comment by many authors. It is regarded as of much shorter heredity than the small bowel and with a function which has been changing in the process of its evolution, so that definite statements regarding the physiology of this portion of the bowel cannot be made which hold true in all instances. In general, it may be stated, however, that the function of the right half of the colon is an absorptive one and that its movements are so regulated that progress of the food is slowed and thorough mixing is assured, thus favoring absorption. In the human being, very little digestion takes place here, although in some herbivora, especially in the horse, there is evidence that considerable takes place. The left portion of the large

intestine has a longer heredity; its functions are likewise more fixed, and in most animals it has been established that this portion acts more or less as a magazine for storage of residue. In general, the contents here are hard and more or less incompressible, whereas those of the right portion of the colon are semiliquid, so a rough division of the functional behavior may be made on this point alone. The mechanical activity of the two portions bears this out as the most distal part acts as a duct through which the contents are evacuated. It is thus seen that primarily the function here is propulsion and expulsion. Besides the motor and absorptive functions, the physiology of the colon includes that of secretion and excretion, the latter being no less important than the others and no doubt linked up with the elimination of poisons and toxins, as well as with the formation of the normal secretions of the colon.

MOVEMENTS OF THE PROXIMAL PORTION

The movements of the large intestine have been investigated by many writers, yet there are many points which still remain unsolved. Researches in this field have been conducted from many angles of approach, such as by the use of an abdominal window, by isolated strips of bowel, by observing the effect of section of nerves, by the use of various diets, by the action of drugs and by the use of pressure methods, such as balloons, and in recent years the use of the roentgen ray with a contrast medium has been invaluable in the study of the physiology of the colon.

After the introduction of roentgenoscopic methods in 1896, attention was drawn to many misconceptions in the field of gastro-enterology and, in a great number of cases, conditions which had formerly been considered anatomic variations were found instead to be normal physiologic movements; consequently, numerous revisions of the concepts of functions of the small and large intestines were necessary.

The first extensive study of the movements of the large bowel seems to have been made by Cannon [3] in 1902, who, by means of the roentgen ray, traced an opaque meal consisting of bismuth subnitrate mixed with salmon through the alimentary tract of the cat. Valuable deductions were made. In the cecum of the animal he found the most common movements to be antiperistalsis, as contrasted to the tonic rings of contraction and propulsive waves in the descending portion of the colon. These waves, he noticed, followed one another like those of the stomach, beginning either at the more advanced portion of the content in the colon or at the nearest tonic constriction, which he observed was frequently found at the termination of the transverse segment of the colon

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3. Cannon, W. B.: The Movements of the Intestines Studied by Means of the Röntgen Rays, Am. J. Physiol. 6:251 (Jan.) 1902.

The first sign of activity was an irregular undulation of the walls of the organ; then faint constrictions passed backward to the cecum. They usually appeared at first only in the region of the ascending colon, but often started near the end of the transverse segment and passed without interruption to the tip of the cecum, where new waves of peristalsis were inaugurated, and these waves finally succeeded in carrying food to the distal transverse colon. The activity was periodic with gradual disappearance of movements in a manner similar to that in which they appeared. Such a period of antiperistalsis lasted usually from four to five minutes and it was repeated at varying intervals, often from three to six times an hour. About twenty-five waves affected any one particle of food so that the result was a thorough mixing of contents, favoring close contact with the absorbing surfaces. These waves in the proximal part of the colon were definitely influenced by psychic factors. Cannon[3] inhibited these movements by holding the cat's nose so it could not breathe, and this in time stopped the movements altogether. There was no cessation of contractions during sleep; likewise, the movements continued during the night. Jacobj,[4] in 1890, seems to have been the first to recognize antiperistaltic movements in the colon, and although he did not describe them in detail, he did state that they seemed to originate from a more or less broad constriction ring. He used cats in which he produced colchicum poisoning, and his studies were made primarily on the small bowel.

Elliott and Barclay-Smith,[5] in a thorough study of antiperistalsis, using etherized animals under saline baths and injecting pea soup into the segments of bowel studied, made observations which in general agreed with those of Cannon. They also classified the different movements of the colon in a manner to explain the varying morphologic differences of that part of the alimentary tube in various mammals. Such difference, they stated, is related to habits of diet and not necessarily to zoologic classification. In the cat they found antiperistalsis, or backward-running waves of constriction, inherent throughout the length of the colon, and not confined to its proximal portion; yet, as a rule, this regressive movement was rarely present except in the ascending, transverse and cecal segments. In the herbivorous animals, such as the guinea-pig and rabbit, in which, as Starling[6] noted, a large part of the process of digestion and absorption goes on in the proximal portion of the colon, the latter is adapted for this, being capacious, with

4. Jacobj, Carl: Pharmakologische Untersuchung über das Colchicumgift, Arch. f. exper. Path. u. Pharmakol. **27**:119 (April 10) 1890.

5. Elliott, T. R., and Barclay-Smith, E.: Antiperistalsis and Other Muscular Activities of the Colon, J. Physiol. **31**:272 (June 30) 1904.

6. Starling, E. H.: Principles of Human Physiology, ed. 4, Philadelphia, Lea & Febiger, 1926.

big absorbent flaps of mucous membrane projecting into its interior. In the guinea-pig, these form a valve between the cecum and the proximal half of the colon which can resist a pressure of several inches of water seeking exit to the colon, but which yields readily to fluid moving with the current of antiperistalsis.

In Elliott and Barclay-Smith's studies on the dog, they never saw antiperistalsis, although the cecum contracted often and with apparently great force, but it did this with complete independence of movements in the other portion of the colon. They consider the cecum in the dog nonfunctional and dwindling, and that the current that has produced it has disappeared. This, in general, is in agreement with Bayliss and Starling's [7] observations, who considered the motor activity of the dog's colon as peristaltic; similar studies by Zondek [8] and also by Lurje [9] on the cat, rat, guinea-pig and other mammals confirmed Elliott and Barclay-Smith's results. Templeton and Lawson,[10] in their studies on the movements of the large intestine of the dog, by a system of balloons, were unable to detect any contractions which they could classify definitely as antiperistaltic.

In 1909, Cannon [11] again carefully studied the movements of the colon and, in corroborating his former observations, attempted to explain the origin and mechanism of antiperistalsis. He regarded the presence of tonic rings of constriction as of significance in the initiation of both peristaltic and antiperistaltic contraction, in substantiation of findings described by Biedermann [12] in 1904. He designated these tonic waves, in the colon as well as in the small bowel, as a persistent shortened condition of the musculature and suggested that it was due to continued excitation. Cannon,[13] in 1911 and 1912, reported further work along this line and emphasized the importance of internal pressure in its influence on movements of the colon. With the presence of a tonic ring

7. Bayliss, W. M., and Starling, E. H.: The Movements and Innervation of the Small Intestine, J. Physiol. **24**:99 (May 11) 1899; The Movements and the Innervation of the Large Intestine, ibid. **26**:107 (Dec. 31) 1900.

8. Zondek, B.: Study of Peristalsis, Arch. f. Verdauungskr. **27**:18, 1920; abstr., J. A. M. A. **76**:346 (Jan. 29) 1921.

9. Lurje, H. S.: Untersuchungen über die motorische Funktion des Dickdarms: IV. Untersuchungen am überlebenden Dickdarm, Arch. f. d. ges. Physiol. **212**:64, 1926.

10. Templeton, R. D., and Lawson, H.: Studies in the Motor Activity of the Large Intestine: I. Normal Motility in the Dog, Recorded by the Tandem Balloon Method, Am. J. Physiol. **96**:667 (March) 1931.

11. Cannon, W. B.: Further Observations on the Myenteric Reflex, Am. J. Physiol. **23**:xxvi, 1908-1909.

12. Biedermann, W.: Studien zur vergleichenden Physiologie der peristaltischen Bewegungen, Arch. f. d. ges. Physiol. **102**:475 (May 21) 1904.

13. Cannon, W. B.: The Relation of Tonus to Antiperistalsis in the Colon, Am. J. Physiol. **29**:238 (Dec.) 1911.

of contraction, the internal pressure on adjacent parts of the intestinal wall is raised, the contraction regions nearby thus being distended and stimulated, with waves passing in each direction. However, he explains that as the contents of the colon are more viscous as they approach the median portion, so in the presence of a tonic ring, with fluid on one side and a viscous mass on the other, the effect would be different. On the side of the latter, the ring could not distend the wall and the wave would not pass distally, but proximally (antiperistalsis). The distal content could be moved by a contraction of the ring, and this is what Elliott and Barclay-Smith saw in the rat and other animals. If the contents were soft, the movements were likely to be antiperistaltic, but if the contents were dry and hard, peristalsis was the usual result, thus showing that the consistence of the feces was of significance in determining the type of movement present. The tonic ring of contraction was maintained after destruction of the spinal cord and, no doubt, the result of increased internal pressure. Balli [14] has enumerated seven definite situations in the colon which, in reality, are spastic areas, although he designated them as sphincters, and further stated that these are the points of origin of antiperistaltic and peristaltic waves. They are as follows: (1) in the ileocecal area; (2) between the cecum and the ascending colon; (3) in the cecocolic area in the proximal segment of the ascending colon; (4) in the transverse colon, at the juncture of its first and third portions; (5) at the splenic flexure; (6) at the juncture of the sigmoid and descending portions, and (7) between the sigmoid and the rectum. Other factors influence these waves, such as intestinal gases, and Henderson [15] has shown that the carbon dioxide content of the blood may be of importance to a certain extent in the activity of the bowel.

In 1918, Alvarez and Starkweather,[16] studying intestinal gradients of rhythmicity, irritability and metabolism, showed that these were present in the colon as well as in the small intestine. They suggested that the herbivora, with their rough, less easily digested, bulky foods and their thin-walled bowel, need a more even gradient than the carnivora. In the cat and the dog, the lower end of the gradient was often reversed, and this may save these animals from frequent calls to defecation. Accentuation of this reversal of gradient, they explain, may be present with some types of constipation.

14. Balli, R.: The Sphincters of the Colon, Radiology **12**:484 (June) 1929.

15. Henderson, Yandell: A Method for the Direct Observation of Normal Peristalsis of the Stomach and Intestines, Proc. Soc. Exper. Biol. & Med. **6**:67, 1908-1909.

16. Alvarez, W. C., and Starkweather, Esther: The Metabolic Gradient Underlying Colonic Peristalsis, Am. J. Physiol. **47**:293 (Dec.) 1918.

Meltzer and Auer[17] watched the intestinal movements through the shaved abdominal wall of the rabbit and saw peristaltic waves, but did not mention antiperistalsis. Likewise, Alvarez[18] stated that in this animal peristaltic waves seem to be very rare.

Thomas and Kuntz[19] observed reversed movements near the cecum in a dog, and Lenz,[20] using a celluloid abdominal window in a cat, definitely established the presence of antiperistaltic waves, regarding them as movements of retention. Likewise, Basler,[21] in 1909, saw churning movements in rats and cats. Groves, in 1909, injected a colored fluid into the rectum of a boy with a cecal fistula and saw this fluid come from the fistula in jets every four or five minutes. It was not in a continuous stream, so he was strongly inclined to the view that antiperistalsis was responsible for the backward movement of this fluid. Smith-Shand[22] saw large antiperistaltic waves in the proximal portion of the colon in a case of obstruction of the colon at the sigmoid flexure, and Schwarz[23] saw a similar type of movement in a patient with chronic constipation.

Further evidence of the presence of antiperistaltic waves in the proximal portion of the colon has been substantiated by experiments in which reversal of a segment of the cecum or ascending portion of the colon has been done. This type of work is similar to that done on the small bowel in which these waves no doubt take place. In 1907, Beer and Eggers[24] reversed 6 inches (15 cm.) of ascending colon and obtained results similar to those found after a similar operation has been done on the small bowel; namely, peristaltic waves descend from the ileum across the upper anastomosis and then along the reversed loop but stop at the distal anastomosis. Circular contractions follow each other in the reversed loop in the same direction as normal peristaltic waves. Likewise, as in the small intestine, the reversed segment of

17. Meltzer, S. J., and Auer, John: Peristaltic Movements of the Rabbit's Cecum and Their Inhibition with Demonstration, Proc. Soc. Exper. Biol. & Med. 4:37, 1906-1907.

18. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, P. B. Hoeber, Inc., 1928.

19. Thomas, J. E., and Kuntz, Albert: A Study of Gastro-Intestinal Motility in Relation to the Enteric Nervous System, Am. J. Physiol. 76:606 (May) 1926.

20. Lenz, E.: Observations à la fenêtre abdominale "colique" du chat: I. Mouvements intestinaux normaux et action péristaltogène des purgatifs anthraquinoniques, Arch. internat. de pharmacodyn. et de thérapie 28:75, 1923-1924.

21. Basler, Adolf: Beiträge zur Kenntnis der Bewegungsvorgänge des Blinddarminhaltes, Arch. f. d. ges. Physiol. 128:251 (May 28) 1909.

22. Smith-Shand, A. K.: Antiperistalsis in the Large Intestine, J. Roy. Nav. M. Serv. 4:367, 1918.

23. Schwarz, Gottwald: Zur Physiologie und Pathologie der menschlichen Dickdarmbewegungen, München. med. Wchnschr. 58:1624 (July 25) 1911.

24. Beer, Edwin, and Eggers, Carl: Are the Intestines Able to Propel Their Contents in an Anti-Peristaltic Direction? Ann. Surg. 46:576, 1907.

colon contains foreign bodies, and dilatation at the upper union takes place where the opposed peristaltic waves meet. Fluid material passes through the loop readily. It is believed that antiperistalsis takes place here, propelling the content of the loop onward, yet the results are not convincing since adaptability of the bowel to new conditions may explain the entire situation. In 1923, Muennich [25] studied antiperistalsis on excluded intestinal segments. He found (contrary to Roith's [26] opinion that antiperistaltic waves cease from the middle transverse portion of the colon downward) that they seemed to be present in the entire organ. He demonstrated a backward flow in cases of ileosigmoidostomy, thus explaining the filling up of the colon back to the cecum and no doubt resulting in the untoward symptoms seen in cases of this nature. Albrecht [27] reported a similar case, and likewise concluded that antiperistalsis in the excluded segment was the explanation of the phenomenon. Blamoutier, [28] in 1925, using roentgenoscopic methods, saw antiperistaltic waves in all portions of the colon except the rectum, and even occasionally noted them in this segment of the large intestine. Cannon, [13] in 1911, stated that reverse movements are present, and that retrogression of feces from the rectum may take place by this movement. It commonly occurs after repression of desire for defecation. However, the rectum may often be full of feces, as Alvarez [18] and other clinicians have found during examinations of the pelves of women, so that retrogression is not always the rule.

The possibility that antiperistaltic movements can be the cause of vomiting has been disputed. Beer and Eggers [24] and Nothnagel [29] stated that vomiting of formed feces and of enemas introduced into a normal gastro-intestinal tract cannot be explained on any other basis. Alvarez quoted a number of authors who have observed the stomach in vomiting and rarely have they observed reversed movements. Alvarez suggested that a general reversal of the intestinal gradient may occur in which the colon takes only a small part.

Colored substances have been injected into the rectum and the subsequent course watched. Bond, in 1905, showed that particles of carmine can travel from the anus back to the cecum and even higher by

25. Muennich, G. E.: Unilateral Intestinal Exclusion, Surg., Gynec. & Obst. **36**:773 (June) 1923.

26. Roith, O.: Ueber die Peristaltik und Antiperistaltik des menschlichen Dickdarmes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **25**:203, 1912.

27. Albrecht, Hans: Zur Frage der Antiperistaltik im Dickdarm bei schwerer Obstipation, München. med. Wchnschr. **59**:1592 (July 16) 1912.

28. Blamoutier, P.: Les mouvements antiperistaltiques du gros intestin, Paris méd. **55**:325 (April 4) 1925.

29. Nothnagel, C. W. H.: Beiträge zur Physiologie und Pathologie des Darmes, Berlin, A. Hirschwald, 1884.

"reverse currents." Grützner.[30] Nothnagel and Starling used similar methods, but their conclusions were against the presence of so-called reverse currents. However, their experiments were performed on dogs, and in these animals antiperistalsis probably does not occur, at least not to any considerable degree.

The introduction into the rectum of an enema, such as saline solutions, by means of the Murphy drip proctoclysis, is followed by transportation by antiperistalsis of the fluid to the proximal or absorbing portion of the large intestine, and explains the disappearance of large quantities of fluid introduced in this manner.

Roentgenographic studies on antiperistaltic movements in the colon of man have contributed much of value. Stierlin,[31] in 1910, and Stierlin and Fritzsche [32] saw reverse transport of feces in the colon of baboons but could detect no such activity in the large intestine of man. Kaestle,[33] in 1912, Serena,[34] in 1913, and Guarini,[35] in 1919, were of the same opinion, after making studies of a similar nature. Schwarz,[36] in 1911, found contractions occurring in an anal as well as an oral direction, but could not determine which were most pronounced. Hertz and Newton,[37] in 1913, by filling the colon with an average-sized opaque enema, saw the fluid run passively to the cecum but with a slight excess. Contractions were stimulated, and the fluid passed in both directions from contracting segmental rings. The latter were associated with a desire to defecate. In agreement with Walsham and Overend [38] and Isémein and Poinso,[39] they were still in doubt as to whether these waves were antiperistaltic.

30. Grützner, P.: Ueber die Bewegungen des Darminhaltes, Arch. f. d. ges. Physiol. **71**:492 (May 4) 1898.

31. Stierlin, Eduard: Ein Beitrag zur radiographischen Untersuchung der Kolonperistaltik, Ztschr.f.klin.Med. **70**:370, 1910.

32. Stierlin, Eduard, and Fritzsche, E.: Verhandl. d. deutsch. Kong. f. inn. Med. **29**:183, 1912.

33. Kaestle: Die Bewegungsvorgänge des menschlichen Dünn und Dickdarmes während der Verdauung auf Grund röntgenographischer und röntgenkinematographischer Untersuchungen, München. med. Wchnschr. **59**:446 (Feb. 20) 1912.

34. Serena, M.: Studio dei piccoli movimenti del colon col seriografio, Atti d. Cong. ital. di radiol. med. **1**:161, 1913.

35. Guarini, C.: Osservazione di movimento colico, Radiol. med. **6**:99, 1919.

36. Schwarz, Gottwald: Zur genaueren Kenntnis der grossen Kolonbewegungen, München. med. Wchnschr. **58**:2060 (Sept. 26) 1911.

37. Hertz, A. F., and Newton, Alan: The Normal Movements of the Colon in Man, J. Physiol. **47**:57 (Oct. 17) 1913.

38. Walsham, Hugh, and Overend, Walker: On the Movements of the Colon, Arch. Radiol. & Electroth. **20**:260 (Dec.) 1915.

39. Isémein, Léon, and Poinso, Robert: Physiologie des côlons, Gaz. d. hôp. **97**:897 (July 5) 1924.

Lenz,[40] in 1919, noted a retrotransport of feces in the colon of man due to a strongly active contraction directed orally, but he did not consider this as identical to antiperistalsis. Case [41] stated that reversed waves are the prevailing type of movement in the proximal colon and that they may become exaggerated in the presence of obstruction lower, thus resulting in stasis in the proximal segment. He called attention to the fact that many writers have described gangrene of the cecum associated with obstruction in the pelvic or sigmoid portions of the colon, and explained the phenomenon as due to waves of antiperistalsis originating at a tonic contraction ring creating back pressure, resulting in distention of the cecum. Blamoutier,[28] in 1925, definitely saw this type of contraction ring from which waves of antiperistalsis seem to arise. He commented on the fact that the ileocecal valve would soon atrophy if it were not for the presence of reverse waves.

Movements other than antiperistalsis take place in the proximal colon. Cannon [42] stated that there are several of these, the first of which he called the serial sectioning movement. This consists of the separation of a small segment in the cecum by a constriction, followed by a second constriction which cuts off another segment just above the first, and with the disappearance of the first constriction, the separated segments unite. A third segmentation then takes place above the second and the changes again occur, thus sectioning the whole mass. Another movement consisting of broad constricting bands appearing and relaxing results in a gentle kneading of the contents. He also noted other movements in the ascending colon, such as strong constricting rings, forcing the contents into the transverse colon. Sometimes these started at the ileocecal valve, but more often they originated in the ascending portion, usually without visible stimulation. Elliott and Barclay-Smith found what they called "propulsive peristalsis" which was present throughout the colon in the animals they studied and which was responsible for the downward movements of the contents.

Holzknecht's [43] opinion was that the colon of man rests most of the time and is active only three or four times each day. He saw masses of feces pass through the colon for a considerable distance almost instantaneously and called them "mass movements."

40. Lenz, Emil: Der retrograde Transport im Dickdarm des Menschen, sein Wesen, seine physiologische und klinische Bedeutung, Arch. f. Verdauungskr. **25**: 54 and 128, 1919.

41. Case, J. T.: Surgical Physiology and Pathology of the Colon from the X-Ray Standpoint, New York State J. Med. **21**:156 (May) 1921.

42. Cannon, W. B.: Peristalsis, Segmentation and the Myenteric Reflex, Am. J. Physiol. **30**:114 (April) 1912.

43. Holzknecht, G.: Die normale Peristaltik des Kolon, München. med. Wchnschr. **2**:2401 (Nov. 23) 1909; The Normal Peristalsis of the Colon, Arch. Roentgen Ray **14**:273 (Feb.) 1910.

These belong more properly to movements of the left half of the colon and will be considered later. Stierlin[31] found that the cecum possessed the least motor capacity of any portion of the colon. Schwarz, in his fluoroscopic work on the large intestine, found that the latter was never at rest but was continually moving and at times capable of very intensive, rapid contractions, leading to considerable displacement of its content toward the anus. The observations of Kaestle, Hertz and Newton, Case, Walsham and Overend, Hertz,[44] Lenz,[46] Lignac,[45] Guarini, Isémein and Poinso, and Blamoutier are of similar nature.

In summarizing the movements of the proximal portion of the colon, it may be stated that this segment is a mixing and absorbing one, and the movements here are not so pronounced or well defined as in the remainder of the large intestine, which is the propelling segment.

Functions of the Haustra and Taeniae.—At this point, it may be well to consider the functions of the haustra. Lineback[46] has made the most recent and most extensive studies on the subject. On the outer surface of the colon there are three lines of thickening of the longitudinal muscle layer called the taeniae, which are well defined in the adult. These are shorter than the colon; so they have the property of decreasing its length and thus causing the intervening parts of the intestinal wall to be drawn or puckered into folds called haustra. Kaestle[33] and Katsch[47] think these folds may be produced by the local constriction of circular fibers, but it is probably true that both factors operate to produce the condition. Lineback, corroborating Lowitz's[48] observations, showed that many small bundles of fibers pass from the longitudinal layers to the circular layers, so that the latter are somewhat thinned in the region of the taeniae. By roentgen studies he noted that the waves of contraction in the circular muscle which produce clefts in each of the three regions between the taeniae occur independently, and rarely do two clefts or zones of contraction occur exactly opposite each other on each side of the taeniae. The effect is usually limited to one region between the taeniae. This is due mainly to the fact that the circular fibers are not strong enough to draw down the taeniae into a

44. Hertz, A. F.: Constipation and Allied Disorders, London, Henry Frowde, 1909.

45. Lignac, Pierre: Les mouvements rétrogrades du colon et leur étude radiologique, Presse méd. **27**:52 (Jan. 30) 1919.

46. Lineback, P. E.: Studies on the Longitudinal Muscle of the Human Colon, with Special Reference to the Development of the Taeniae, Contrib. Embryol. **11**: 35, 1920.

47. Katsch, Gerhardt: Der menschliche Darm bei pharmakologischer Beeinflussung seiner Innervation, Fortschr. a. d. Geb. d. Röntgenstrahlen **21**:159, 1914.

48. Lowitz, G. A.: Recherches sur l'appareil musculaire du gros intestin chez l'homme et quelques mammifères, Thèse de Bordeaux, no. 41, 1896, p. 32.

stomach and small bowel. Elliott and Barclay-Smith, studying the mechanisms of antiperistaltic waves, presumed them to be immediate myogenic responses to distention and correlated them to the churning movements of the small bowel. Alvarez's gradient idea explains the phenomena of movements in the colon in a logical manner. The ileo-cecal sphincter normally has a gradient of irritability higher than that of the ileum, thus explaining backward reflection of waves over the ileum, the sphincter functioning as an effectual barrier. The muscle of the colon is more sluggish than that of the ileum, and segments of the tip of the cecum were less irritable than those from the base. In studying the movements of the cecum, he found the gradient to be upward from the base of the cecum, through to the remainder of the colon, thus explaining its reservoir function. He showed that normally the tone of the rectum and sigmoid is higher than that of the colon immediately above; this he noted to be helpful in keeping fecal matter from packing up against the sphincter, and this explains how sometimes feces are returned to the upper part of the colon when defecation is postponed. Defecation can be readily supposed to take place when the gradient above becomes so steep or that of the sigmoid and rectum so lowered that the fecal material moves downward. In a similar manner, interference or an abnormal gradient may explain constipation, postoperative ileus, vomiting, gastric dilatation and dyspepsia.

Studies of Movements of the Colon with Various Types of Enemas. —The introduction of the opaque enema along with roentgenoscopy or fluoroscopy, and the use of other types of enemas, have afforded an important means of studying the physiology of the colon. Cannon,[3] in 1902, made many observations, using roentgenographic methods, and thought that enemas in general stimulated antiperistalsis of the colon; the movements sometimes lasted over an hour, but usually they were not strong enough to force the contents through the ileocecal valve unless the enemas were very large. However, he once saw these waves in a normal subject, after using an extremely small enema, so came to no definite conclusions. In the cat a small enema of 25 cc. of the opaque mixture first lay in the descending colon; then reverse waves were soon set up and the material was forced back into the cecum, but nothing went through into the small intestine. With from 90 to 100 cc., it was often observed to pass through the ileocecal valve. Schwarz,[23] in 1911, found that considerable stimulation to contraction of the colon was obtained by use of various enemas, and his observations in human beings were similar to those of Drummond,[56] who noted that enemas rarely go beyond the cecum; in other words, the ileocecal valve was usually com-

56. Drummond, Hamilton: Observations on the Functions of the Colon, with Special Reference to the Movements of Enemata, Brit. M. J. **1**:240 (Jan. 31) 1914.

petent. Hertz[11] found that if more than 750 cc. of fluid was used in human beings, the colon contracted and expelled the contents, and he thought that hydrostatic pressure alone brought about passage of fluid to the cecum. Drummond tried this on cadavers and found that the fluid passed backward just as rapidly as in the living person.

Joltrain, Baufle and Coope[57] produced pressure of various kinds in the large bowel and noted the effects. They found that the normal colon can hold about 1,000 cc. of fluid, which they computed was under a pressure of from 16 to 20 cm. height of water and created no distress. With various diseases of the large intestine the capacity was much less and the pressure under which it was retained was much greater. When the pressure rose to around 30 cm. of water, with a volume of 3,000 cc. in the colon, the patients complained of pain and distress. Burt[58] determined the pressure required to rupture the bowel at various levels by the introduction of air. He found the rectum to support the greatest average pressure, with the sigmoid, ileum, esophagus, jejunum, transverse colon, cecum and stomach in order of their rupture. The greatest pressure supported was 11.59 pounds per square inch. In the rectum of a child, aged 11 years, and in adults, the average was around 8.36 pounds per square inch. The practical application of Burt's work lies in the emphasis of care in instrumentation in proctology, in administration of enemas and in the breaking up of impacted fecal masses. Friedenwald and Feldman,[59] in 1931, studied the detrimental effect of prolonged use of various enemas. Using tap water once daily for one hundred and fifty-five days, they saw a few hemorrhagic areas in two of three animals; with soap, only one of three had this appearance; with cotton seed oil, there were no changes, but with a solution of sodium bicarbonate, the typical clinical and pathologic picture of chronic ulcerative colitis was produced in each of the animals observed.

Betz found reflex contraction of the large intestine after the injection of a glycerin enema as high as the hepatic flexure, and Alvarez's view is that many times the effect may go much further. He voiced the experience of others in noting that patients occasionally become nauseated from ordinary injections of physiologic solution of sodium chloride and vomit when anything a little more irritating is introduced, such as soap, glycerin, turpentine or dextrose. This also gives founda-

57. Joltrain, E.; Baufle, P., and Coope, R.: Essai de mesure de la pression du gros intestin. Ses variations. Application a la clinique. Bull. et mém. Soc. méd. d. hôp. de Paris **43**:211, 1919.

58. Burt, C. A. V.: Pneumatic Rupture of the Intestinal Canal with Experimental Data Showing the Mechanism of Perforation and the Pressure Resisted. Arch. Surg. **22**:875 (June) 1931.

59. Friedenwald, J., and Feldman, M.: Experimental Studies on the Effects of Prolonged Use of Colon Enemas upon the Bowels in Animals, Am. J. Surg. **11**: 23 (Jan.) 1931.

tion for the opinion that part of the nausea and distress, and even of the vomiting, following abdominal operations may be due to the use of the Murphy drip type of apparatus for rectal instillation of fluids, and, in fact, several authors have commented on this. Rolleston and Jex-Blake [60] noted that in a series of ninety-six patients with gastric disturbances who were fed by rectum, twenty-six vomited at some time or other, and Bine and Schmoll [61] advised against the use of enemas in the presence of fecal vomiting, because in this condition any fluids instilled in the rectum would be liable to be vomited. The explanation of the phenomenon, as Alvarez stated, is a reversal of the normal gradient, with waves traveling in the opposite direction, due to the stimulation of the lower end of the tract by the irritating enemas.

The movements of the colon were studied by the authors with a tandem set of three balloons in the isolated large intestine of the dog. In this type of preparation in which nearly normal conditions were maintained, the ileum was connected to the sigmoid as closely as was anatomically possible and the two ends of the colon were brought out as in cecostomy and sigmoidostomy, respectively. In this manner, the influence of anesthesia as well as operative trauma could be excluded. Kymographic tracings were made of the movements by the use of small balloons connected to a water manometer system. The position of the balloons as checked at postmortem examination was found to be in the cecum, at the splenic flexure and in the lower part of the sigmoid. By administration of various cathartics through the stomach, definite activity could be elicited in this isolated loop such as that accompanying defecation, vomiting or the gastrocolic reflex.

One of the most evident facts that impresses one in this study is the marked difference in activity between the cecum and the remainder of the colon. The cecum was constantly active and from these movements of mixing and churning it could easily derive its important function of absorption. Whether these contractions are antiperistaltic or peristaltic, or whether they are the result of local stimulation was difficult to determine, but at any rate they were definitely of different character than those of the distal portion of the colon. They seem to represent a higher degree of irritability than is found elsewhere in this organ. Normally the distal part of the colon was almost completely inactive, showing only small, almost imperceptible contractions which probably were the effect of respiration. However, when activity did take place the most frequent movements were systolic pulsations and not peristaltic waves. The latter type of contraction was rarely definitely identified.

60. Rolleston, H. D., and Jex-Blake, A. J.: On the Occurrence of Vomiting During Rectal Alimentation., Brit. M. J. 2:68 (July 11) 1903.

61. Bine, René, and Schmoll, Emile: The Treatment of Gastric and Duodenal Ulcer, California State J. Med. 12:361 (Sept.) 1914.

Many authors have found the colon never inactive but continually showing some degree of motility. These movements of the large intestine indicate a high degree of efficiency which has been developed, and show the adaptations of this organ to mechanical conditions which are present. The activity of the cecum promotes absorption and aids in retaining the fecal material until the consistence is such that it acquires form and is then pushed on though the transverse colon to the splenic flexure. From here it is transported by coarser movements and undergoes little change until it is expelled. Disturbances in this absorptive or expulsion function, such as retaining the feces in a liquid state throughout, or on the other hand, drying them too much, may account for some cases of diarrhea and of constipation, as many authors have suggested.

It is a common clinical observation in patients with diarrhea that after eating there are abdominal distress, cramps and the urge to evacuate the bowels, and also that the patient is definitely more comfortable between meals. There seems to be no doubt that there is a definite relationship between the ingestion of food and defecation in both normal human beings and animals. In the present series of experiments on the so-called gastrocolic reflex, the latter was definitely elicited in spite of the fact that there was lack of continuity in the intestinal tract between the stomach and colon, so that the possibility of an impulse running down the bowel by either neurogenic or myogenic means to stimulate the colon must be eliminated. In this connection, Alvarez quoted Short,[62] who noticed that the coils of the ileum were always active except during fasting, but when food was taken little gushes of succus entericus appeared at the ileocecal sphincter in from one and a half to four minutes. Likewise Cannon,[13] in 1911, showed that as food enters the cecum a fresh series of waves is initiated there Lyman [63] further demonstrated what he called a "receptive relaxation" of the colon when food entered it from the ileum, similar to that of the cardia as its contents pass through the esophagus. He also noticed that as soon as the small bowel had finished emptying itself through the ileocecal sphincter and had again become quiet, the large intestine became active. His explanation is that there was reciprocal innervation of the two portions of the bowel. Surmont, Dubus and Tiberghien [64] sectioned the ileum near the cecum and could produce movements in

62. Short, A. R.: Observations on the Ileo-Caecal Valve in Man, Brit. M. J. **2**:164 (Aug. 9) 1919.

63. Lyman, Henry: The Receptive Relaxation of the Colon, Am. J. Physiol. **32**:61 (May) 1913.

64. Surmont, H.; Dubus, A., and Tiberghien, P.: Contractions coliques consécutives a des excitations prépyloriques et duodénales, Compt. rend. Soc. biol. **71**:641, 1911.

the colon by irritation of the stomach. Likewise, Alvarez, in 1924, cut
the bowel across and found that although no waves crossed this opening,
yet simultaneous movements took place in many parts of the intestine,
and he was of the opinion that nerves in the mesentery served to carry
these impulses. The mechanism of the gastrocolic reflex he explained
on a similar basis; this seems the most reasonable in accounting for the
presence of this type of activity in the colon in this series of experiments.

MOVEMENTS OF THE DISTAL, OR LEFT, HALF OF THE COLON

The movements of the left half of the colon are antiperistalsis,
which most investigators agree takes place, at times especially, in con-
nection with a similar type of activity in the right half of the colon, and
coordinated peristalsis, which drives the content onward, similar to that
of the small bowel. Several other types of movements in the colon have
been reported. The best understood of these are the strong contractures
which evacuate the bowel. Elliott and Barclay-Smith noted that these
were slow, powerful constrictions of the tube commencing at a point a
considerable distance up the colon and running downward to empty the
contents, an action common to all animals and a fundamental reaction to
stimulation of the sacral nerves. Most of our knowledge of the move-
ments of the colon has been gained by means of roentgenograms, either
an opaque meal or an opaque enema being used.

Cannon,[3] in 1902, found that as the content from the proximal colon
was pressed gradually onward toward the transverse and descending
portion of the colon, a deep constriction appeared near the advancing
end and almost separated a globular mass from the main body of food.
The contents progressed farther along the colon, and new tonic con-
strictions appeared which separated the contents into globular masses.
As these increased in number, they got farther from the cecum, although
they were present chiefly in the descending colon. Raiser [65] recorded
similar observations in the colon of the rabbit, in which deep circular
constrictions separated the scybalous masses. Thus, as Cannon [13] brought
out, these rings of constriction, moving slowly from the cecum, pushed
the hardening contents before them. It is obviously an advantage to
have them pushed through in divisions rather than in a uniformly
cylindric mass, and while this is going on, some absorption takes place
within the confines of these rings. Kaestle explained the facility with
which the contents of the colon were moved forward as due to an
advancing column of gas which opened up the lumen of the bowel
before it.

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65. Raiser, K. P. T.: Beiträge zur Kenntnis der Darmbewegungen (Giessen).
Worms am Rhein, A. K. Boeninger, 1895.

Schwarz added that increased abdominal pressure was of considerable significance in moving the fecal material along the colon, and that in constipation and in stenotic lesions of the bowel he could see the segmentation contractions somewhat accentuated, and even hypermotile, depending on the degree of occlusion of the lumen of the bowel. Serena, in 1913, made similar observations, and Bergmann[66] and Schwarz noted that contractions were markedly activated under the influence of distending enemas. Walsham and Overend stated that these movements are due to true peristaltic waves, with a rate of from one to two a minute, and that they are abolished by nicotine or curare and probably originate from nodal tissue. Walsham and Overend described smaller rhythmic contractions with waves coming at the rate of about twelve each minute, which they claimed had no directive power but exhibited periodic augmentation and were either purely myogenic or myoneurogenic. These were practically identical to those observed by Isémein and Poinso. Hurst,[67] in 1922, found that the tonus and movements of the colon depend largely on the bulk of its contents, and these varied continuously with the amount of gas and feces present. He also observed that the descending and pelvic portions of the colon were usually empty and consequently in a state of tonic contraction with more or less obliteration of its lumen, whereas the opposite condition was present on the right side. Here the content was fluid or semifluid, the tonus was less and the lumen greater, so that he considered it normal to find a large splashy cecum when the portion of colon felt on the left side gave the impression of a solid cord. From his roentgenologic observations on human subjects, he noted that the colon was quiet most of the time and only changed materially after hours in which a meal was taken.

Hickey[68] found the movements of the colon by the barium sulphate enema so slow and so infrequent that opportunities to observe them were rare, and in most cases, whether the colon is filled by a barium meal or by a barium enema, the examiner can report only the size, shape and relation of the component parts of the large intestine. However, by overdistending the organ with large enemas of opaque material he saw peristalsis begin in the transverse colon and pass along to the splenic flexure, forcing the content onward and distending the upper portion of the descending colon. The content may be interrupted temporarily here but it soon passes on, emptying the lower portion of the descending colon and starting up peristaltic waves in the sigmoid which may result in

66. Bergmann, quoted by Schwarz.[36]

67. Hurst, A. F.: Sins and Sorrows of the Colon. Brit. M. J. **1**:941 (June 17) 1922.

68. Hickey, P. M.: Peristalsis of the Colon. Am. J. Roentgenol. **9**:269 (April) 1922.

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evacuation. About this time peristalsis starts in the cecum, emptying it rapidly and passing onward to the transverse colon where the procedure again takes place. Flint [69] holds an opinion similar to that of Hickey in that he found the colon quiet most of the time except after meals, and Murray [70] stated that normal peristalsis does not take place until the colon is full. Macleod [71] regards the descending colon as a tube for the transferring of masses from the transverse colon; he claims it is never distended. Rokitansky, in 1842, stated that this portion of the colon is normally empty. This fits in well with the study of Gleize-Rambal,[72] who observed that there is a line of demarcation between the transverse and descending portions of the colon which makes the distal colon well suited for strong muscular efforts to evacuate it. The descending portion is smaller and rounder and maintains its shape with greater ease than the transverse portion which is large, thin-walled and transparent. Microscopically, the muscularis of the descending portion is thick, and that of the proximal portion is poor in longitudinal fibers. He also found the cellular structure denser and thicker on the transverse portion with correspondingly greater amounts of mucus in this region. His observations were made on cadavers, at laparotomy and roentgenographically. Similarly, Kirkes [73] found that the muscular fibers of the colon become stronger as they progress distally, and are strongest in the rectum where greatest tension is exerted. Schellberg [74] considered the attachment of the colon at the hepatic and splenic flexures as important in the performance of their movements, which, he stated, are deliberate and seldom take place. Mills [75] described three movements of the colon expressed in relation to the colonic rugae, in which Forsell [76]

69. Flint, Ethelbert: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) **15**:54, 1922.

70. Murray, D. H., in discussion on Beach, W. M.: The Subnormal Function, J. A. M. A. **71**:1453 (Nov. 2) 1918.

71. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, ed. 5, St. Louis, C. V. Mosby Company, 1926.

72. Gleize-Rambal, L.: Sur l'individualité anatomique du côlon descendant, Compt. rend. Soc. de biol. **99**:2015, 1928; L'individualité structurale du côlon descendant, ibid. **100**:368, 1929; Note sur la disposition du gros intestin de l'embryon humain du 3e mois, ibid. **100**:715, 1929.

73. Kirkes, W. S.: Handbook of Physiology, ed. 16, New York, William Wood & Company, 1900.

74. Schellberg, O. B.: Observations on the Physiology of the Human Colon, Internat. J. Med. & Surg. **41**:40 (Jan.) 1928.

75. (a) Mills, A. E.: Some Effects of Disturbance of Physiology of Movements of Gastro-Intestinal Tube, M. J. Australia **1**:127 (Feb. 7) 1925. (b) Mills, R. W.: Studies of the Colon: I. Roentgen-ray Evidence of Colonic Secondary Changes, Am. J. Roentgenol. **11**:487 (June) 1924.

76. Forsell, quoted by Mills.[75 b]

agreed. These, he stated, are: (1) the lateral or nonhaustral canalicular, (2) the general polydirectional haustral and (3) the longitudinal haustral compression movements.

Lenz [20] studied the movements of the colon of the cat through a celluloid abdominal window; Katsch and Borchers [77] have described the technic of this method in detail and saw two types of propulsive movements, annular and tubular, which were entirely distinct from those of defecation. Zondek,[78] in 1921, made a similar study of various animals and observed peristaltic movements occurring with considerable regularity in the dog about every thirty seconds; these were markedly stimulated by the taking of food. He also described haustral segmentation by a similar means in the colon of rabbits, and antiperistalsis as the usual finding in the proximal portion of the large intestine in the cat, rat, guinea-pig and other mammals. Plant and Miller,[79] using balloons in the colons of unanesthetized dogs, observed waves similar to those obtained by Templeton and Lawson. The latter investigators used a tandem set of six balloons in the dog's colon, three of which were inserted through a cecostomy opening and three through the rectum, and obtained some excellent records of the character of the movements of the large intestine. With this preparation simultaneous tracings were made of the entire colon. In the proximal portion, activity was distinctly periodic with contractions superimposed on changes in tonus, whereas in the distal portion changes in tonus were less pronounced but otherwise similar. The point at which the change took place was at the splenic flexure. They also found that the entire colon could act as a unit, but that the activity was subject to sudden alterations in the formation of waves going in either direction. In general, their results confirm those of other investigators.

Mass Movements.—One of the most interesting and frequently disputed movements of the colon is the so-called mass movement, it was described by Hertz [80] in 1907 and 1908, Hertz, Cook and Schlesinger [81]

77. Katsch, Gerhardt, and Borchers, Eduard: Beiträge zum Studium der Darmbewegungen. I. Das experimentelle Bauchfenster, Ztschr. f. exper. Path. u. Therap **12**:225 (Jan. 8) 1913.

78. Zondek, B.: Ueber Dickdarmperistaltik, Beobachtungen am experimentellen Bauchfenster, Arch. f. Verdauungskr. **27**:18, 1920; abstr., J. A. M. A. **76**:346, (Jan. 29) 1932.

79. Plant, O. H., and Miller, G. H.: Effects of Carminative Volatile Oils on the Muscular Activity of the Stomach and Colon, J. Pharmacol. & Exper. Therap. **27**:149 (March) 1926.

80. Hertz, A. F.: The Pathology and Treatment of Chronic Constipation, Proc. Roy. Soc. Med. (Sect. Med.) **1**:119, 1908.

81. Hertz, A. F.; Cook, F., and Schlesinger, E. G.: The Action of Saline Purgatives, Guy's Hosp. Rep. **63**:297, 1909.

in 1909, Holzknecht in 1909, Barclay [82] in 1912 and Kaestle in 1912, and later by many others. Previous to the paper by Holzknecht in 1909, there seems to be no detailed statement concerning the mechanics of the propulsion of the fecal content over considerable areas, and credit should be given him for recognizing and describing these movements in detail. In brief, this movement is as follows: It is the principal normal propulsive movement of the colon taking place three or four times a day, serving to move the contents of the bowel from the anti-peristaltic influence of the proximal portion of the colon through to the distal portion. The mechanism, as Holzknecht explains, may possibly be a powerful peristaltic wave, but more likely is associated with a tonic contraction of the circular coat of the part of the colon through which the wave passes. The haustral markings disappear and fecal matter seems to run together in a sausage-like bolus, which has smooth edges and is rounded at the ends. The mass at once begins to move at about twice the rate of peristaltic waves in the stomach, and the rate and distance of this movement are variable, sometimes transporting the fecal content from the cecum to the pelvic colon or rectosigmoid without stopping. When it comes to rest, haustral indentations reappear. Alvarez observed these mass movements often secondary to a rush wave in the small bowel and frequently resulting in a call to defecation. According to Case, they are most often seen before or during defecation. These movements are accompanied by a gurgling sound, due, Kaestle stated, to the accumulation of gases in advance of the moving mass, and expanding the colon ahead, thus facilitating movements over long distances. Diarrheal cramps, Case stated, are often accompanied by mass movements, and Alvarez saw these contractions in patients with a tendency to diarrhea. Kaestle noted these movements in a woman; the entire colon took part, contracting down to the size of a cord, but it was so marked and long continued, as well as accompanied by such severe spasmodic pain, that he concluded it was due to a disorder of innervation of the colon. Hertz,[44] in 1909, and also Welch,[83] in 1925, noted perceptible progress through the colon after meals, but otherwise this was very slow. Barclay,[84] in 1911, 1912 and 1913, studied these movements carefully and blamed defects in mechanism of this type of activity as resulting in stagnation in the rectum and other parts of the colon, and being one of the causes of constipation. In a further study in

82. Barclay, A. E.: Note on the Movements of the Large Intestine, Arch. Roentgen Ray **16**:422 (April) 1912.

83. Welch, P. B.: What Constitutes Constipation: Some Observations on Colon, J. Iowa M. Soc. **15**:18 (Jan.) 1925.

84. Barclay, A. E.: Radiological Studies of the Large Intestine, Brit. J. Surg. **2**:638, 1914-1915. Barclay [82].

1909 and again in 1913, Hertz,[85] and also Betz, in 1912, corroborated Holzknecht's view and added that the chief stimulus to this movement is entry of food into the stomach, and designated it as the gastrocolic reflex. Holzknecht, incidentally, noted the mass contraction after feeding a second bismuth meal. Hertz [44] further observed that normally the ileocecal sphincter held back the content in the terminal ileum for a considerable time, relaxing principally during meals, at which time the greater part of the content entered the cecum. Peristalsis in the lower part of the ileum became more activated at meal time. Hertz and Newton, in 1913, saw the phenomenon in a patient with partial intestinal obstruction due to carcinoma of the rectosigmoid juncture, and noted that the contents of the colon passed from one end to the other in a second or two, with no signs of either peristalsis or antiperistalsis.

Isémein and Poinso explained the mechanism of the gastrocolic reflex as consisting either of stimulation of the colon by a hormone from the gastric mucosa or of stimulation of the circular muscles of the small intestine down from the stomach and extending to the large bowel. Likewise, Betz, in 1912, considered the stomach and rectum as the principal reflex routes for stimuli to the intestine. Alvarez regarded the gastrocolic reflex as involving the mesenteric nerves.

In 1916, Walsham and Overend reported observations on sporadic mass movements following chiefly either the entrance of food into the empty stomach or evacuation of the bowel, and again in 1922, Hurst corroborated these observations, stating further that after the absorption of water from the contents of the right half of the colon the fecal matter is moved from the cecum to the pelvic colon, where it remains until mass movement carries it farther. They found that during the day the greater part of the cecal, ascending and pelvic portions of the colon are more or less full and the remaining part is empty. In a careful study, Welch and Plant,[86] using balloons placed in the stomach and colons of dogs through fistulas, and in the colons of human subjects, obtained tracings. Their observations showed that the normal muscular activity of the colon is very irregular and great variations in tonus and contractions occur, with the colon never in the state of complete inactivity which Holzknecht found. After feeding the dogs, they obtained a definite increase in tonus of the colon in from half a minute to several minutes, lasting from ten to twenty or up to sixty minutes. Sometimes this reaction would be repeated several times, but more often there was no second effect. By feeding through a fistula in the stomach, such results were not obtained. They therefore claimed that to call this

85. Hertz, A. F.: The Ileo-Caecal Sphincter, J. Physiol. **47**:54 (Oct. 17) 1913.
86. Welch, P. B., and Plant, O. H.: A Graphic Study of the Muscular Activity of the Colon, with Special Reference to Its Response to Feeding. Am. J. M. Sc. **172**:261 (Aug.) 1926.

reaction a "gastrocolic reflex" was a misnomer and that it is really a "feeding reflex" or "appetite reflex," similar to that of gastric secretion, depending not on distention of the stomach with food but more on psychic stimulation. They further substantiated this opinion by obtaining a typical result with merely the entrance of the attendant who usually fed the dog. They also demonstrated that with an empty bowel the effect was much less or was even absent, as contrasted to that obtained when the bowel was full. Schellberg, in 1928, considered the presence of gas as important in mass movements, and also that chemical activity of the fecal content on the mucosa played a considerable part in this and other types of movements of the colon. Draper and Johnson [87] disagree with former opinions of mass movements and stated that propulsion of the contents of the colon takes place by slow imperceptible segmentation contractions and probably not by so-called "mass movements" which they were never able to see. Hines, Lueth and Ivy,[88] in 1929, put balloons into the rectums and sigmoids of human subjects, through a proctoscope. They found two definite types of curves, one a slow, slight rhythmic elevation with a tonus rhythm and the other steep contractions. Among twenty-one normal students they obtained a steep contraction in five only after meals, and this was concomitant with an urge to defecation. They felt this was probably the gastrocolic reflex of other investigators. Such urge was not present if the subjects were constipated, and steep waves could not be obtained at any time with similar technic. They concluded, therefore, that the threshold for sensation in cases of constipation is raised. They also concluded that, the latter type of movement is an involuntary aid to defecation. Movements similar to the mass contraction of Holzknecht were obtained by Ganter and Stattmüller.[89] Using a balloon in the colonic stoma of a patient with chronic ulcerative colitis, they obtained high contractions in groups similar to those obtained by Hines, Leuth and Ivy. Peiper,[90] by putting a double balloon in the distal colon of children, found that usually there was no activity, although if diarrhea was present there was a pendular type of movement.

   Defecation.—Cannon,[3] in 1902, observed the process of defecation by roentgenographic means and described it as a slow, sweeping move-

   87. Draper, J. W., and Johnson, R. K.: The Pathogenic Colon: Recent Studies, Am. J. Surg. 4:1 (Jan.) 1928.

   88. Hines, L. E.; Lueth, H. C., and Ivy, A. C.: Motility of the Rectum in Normal and Constipated Subjects, Arch. Int. Med. 44:147 (July) 1929.

   89. Ganter, G., and Stattmüller, K.: Studien am menschlichen Darm: III. Ueber die normalen Dickdarmbewegungen des Menschen und ihre Beeinflussung durch Pharmaka, Ztschr. f. d. ges. exper. Med. 42:143, 1924.

   90. Peiper, Albrecht: Bewegungen des Magen-Darmkanals im Saüglingsalter. 4. Der Dickdarm, Jahrb. f. Kinderh. 120:312, 1928.

ment in which the bowel swung around so that the ascending colon lay in the position of the distal half of the transverse portion, and the latter took the position of the descending part. At the same time tonic contractions disappeared and were replaced by strong, broad contractions of the circular muscle, tapering the contents off on each side *into two cones.* As the intestine swung around, more material *was forced into the rectum by constriction,* dividing the lumen, which passed slowly downward aided by the abdominal musculature. Usually some material was left behind in the cecum. Hertz [44] described this act as consisting of contractions of the diaphragmatic and abdominal muscles which resulted in a considerable increase in pressure in the abdomen since the glottis was kept closed, aiding in forcing more feces into the rectum. Through the stimulation thus produced in the rectum, involuntary peristalsis starting well back in the colon was initiated. Included in this chain of reflexes was inhibition of the internal sphincter. His impression was that the entire colon took part in the act, but that only the bowel distal to the splenic flexure was evacuated, and in some cases even the rectum was not completely emptied. The content of the right part of the colon moved over to the descending colon to take the place of that which was evacuated. Schwarz's [28] observations were of a similar nature, except that he saw fecal masses go through almost the entire length of the colon and this movement was associated with contractions of that organ. By the introduction of stimulating enemas he demonstrated a similar proce s, and could by this method obtain evagination and invagination of the haustra. He further demonstrated roentgenologically that prior to, and during, defecation there regularly occurred coarse movements of the large intestine. These occurred typically as cramps and were often associated with diarrhea. Schwarz [23] attributed propagation of intestinal contents to the fine and coarse movements of the large intestine and also to the increased intra-abdominal pressure. In this connection it may be noted that Jonas,[91] in 1912, found in his studies on achylia gastrica that diarrhea was associated with a hypermotility of the entire gastro-intestinal tract and not necessarily of the large bowel alone. Also, he noted that if the propulsion of the contents was abnormally fast in the small intestine, a normal stool could still result, providing there was a delay in the passage through the distal portion of the colon.

There probably is no distinct desire to empty the bowels until feces have actually reached the rectum and produce distention there, as Howell has pointed out, and as Hertz and Newton, in 1913, were able to see roentgenographically. The feces are retained by tonic contraction of the

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91. Jonas, Siegfried: Ueber das Verhältnis zwischen Stuhlbild und Darm tilität und die wechselnden Stuhlbilder der Hyperacidität und der Achylie, Arch f. Verdauungskr. **18:**769, 1912.

internal sphincter until defecation begins, then the sphincter relaxes and masses are forced through the anal canal by the combined efforts of the rectal and abdominal muscles. In other words, it is normally both a voluntary and an involuntary action. The minimal pressure within the rectum found by Hertz [44] to initiate a call to defecation was between 3 and 4 mm. of mercury, and the pressure within the rectum may become from four to eight times that much during the act as a result of the increased intra-abdominal pressure. The latter then caused more material to enter and to distend the rectum, and resulted in still stronger contractions of abdominal and rectal muscles as well as a corresponding relaxation of the internal sphincters. Severe pain may be produced by using extreme distention in the colon, as Fröhlich and Meyer [92] have shown. They attributed this either to spasm of the circular musculature or to irritation of the peritoneal coat. Alvarez noted a tendency sometimes in man to empty the rectum completely by a process of prolapse and eversion of the mucous membrane, and Starling stated that the last section of the rectum is emptied at the close of defecation by forcible contractions of the levator ani and other perineal muscles, contractions which serve to restore the everted mucous membrane. Luciani considered peristaltic activity of the sigmoid and rectum as most essential in the act of defecation, although inhibition of tone of the internal sphincter, contractions of the levator ani and abdominal compression by contractions of the diaphragm and abdominal musculature along with closure of the glottis are important factors.

A spurious desire to move the bowels may be aroused by pressure from external sources on the walls of the rectum, such as from a large calculus of the bladder, prostatic tumor or fetal head in the pelvis. The same effect may be noticed from internal hemorrhoids, tumor of the rectum or an inflammatory disease present in that region.

Defecation may be restrained by several muscles or combinations of muscles, such as the internal sphincter, the external sphincter, the levator ani and the voluntary muscles about the perineum, as Frankl-Hochwart and Fröhlich [93] pointed out.

There are other factors which influence or take part in the act of defecation, namely, centers in the brain and spinal cord. Hatcher and Weiss, [94] in 1923, applied small doses (0.016 mg.) of picrotoxin to an area in the floor of the fourth ventricle close to the vomiting center and produced diarrhea almost immediately, and Luciani, in 1913, found

92. Fröhlich, A., and Meyer, H. H.: Die sensible Innervation von Darm und Harnblase, Wien. klin. Wchnschr. 25:29 (Jan. 4) 1912.

93. Frankl-Hochwart, L., and Fröhlich, Alfred: Ueber Tonus und Innervation der Sphinkteren des Anus, Arch. f. d. ges. Physiol. 81:420 (Aug. 11) 1900.

94. Hatcher, R. A., and Weiss, Soma: Studies on Vomiting, J. Pharmacol. & Exper. Therap. 22:139 (Oct.) 1923.

areas in the brain where stimulation affected the tonus of the sphincters. However, it is probable, as Alvarez stated, that the most important centers for the sphincters are in the third and fourth sacral segments of the cord. This was substantiated by Goltz,[95] and also by Goltz and Ewald's [96] observations that immediately after destruction of the lumbar and sacral cord in dogs, the anus was relaxed and gaping. Occasionally there was diarrhea, but this gradually cleared. In time defecation became normal and there was no atrophy of the sphincter, showing that the rectum and sphincters act by virtue of their own intrinsic mechanism, a faculty which Alvarez attributed to the high autonomy of the rectum.

When there is nothing to start the chain of reflexes which brings about defecation, such as loss of sensation in the rectum, it is then that the most severe disturbances are produced. Merzbacher,[97] in 1902, demonstrated this by cutting the sensory roots of the three sacral nerves of the dog. The animals were not aware of anything in the rectum because of the anesthesia produced. The feces became dried out, no attempt was made by the animal to defecate, and it was only when a considerable amount of material collected in the rectum that it was pushed out passively. This is likewise true in human subjects, as noted by Bálint and Benedict,[98] in 1905 and 1906, who studied six cases of lesions of the conus terminalis and found that the patients were generally constipated in spite of relaxation of the anal ring and anesthesia of the mucosa of the rectum. However, they could control the bowel movements fairly well. These observers made no roentgenographic observations of the colon. McIntosh,[99] in 1929, confirmed this in observing a child, aged 6 years, with a lesion of the spinal cord in the lumbosacral area. He found marked stasis of the colon; it took a barium meal twelve days to reach the rectum and longer to be expelled. It took ten days for it to pass from the splenic flexure down so that most of the retardation was in the left portion of the colon. The tonus of the large bowel was apparently good, the haustra appeared normal, and there was no localized atony or dilatation. McIntosh agreed with other observers in that it seemed to him that the trouble was chiefly

95. Goltz, F.: Ueber die Functionen des Landenmarks des Hundes, Arch. f. d. ges. Physiol. **8**:460, 1874.

96. Goltz, F., and Ewald, J. R.: Der Hund mit verkürzten Rückenmark, Arch. f. d. ges. Physiol. **63**:362, 1896.

97. Merzbacher, L.: Die Folgen der Durchschneidung der sensibeln Würzeln im unteren Lumbalmarke, im Sacralmarke und in der Cauda equina des Hundes, Arch. f. d. ges. Physiol. **92**:585 (Nov. 5) 1902.

98. Bálint, R., and Benedict, H.: Ueber Erkrankungen des Conus terminalis und der Cauda equina, Deutsche Ztschr. f. Nervenh. **30**:1 (Dec. 20) 1905.

99. McIntosh, Harriet C.: Roentgenologic Study of the Colon in a Child with a Spinal Cord Lesion, Am. J. Roentgenol. **22**:247 (Sept.) 1929.

sensory impairment of the rectum and that there was no excitant to initiate mass movements. Also, there was no sudden entry of a large amount of material into the rectum as there is when mass contractions take place. Peculiarly enough, it is the experience of neurologists that there is no definite relationship between the level of the situation of a tumor of the spinal cord and the degree of disturbance of sphincter function.

The fact that most people perform the act of defecation in the morning soon after breakfast is generally ascribed to several factors. During the night the contents of the colon are gradually moved from the proximal to the pelvic and descending portions, and after being comparatively quiet the large bowel is stimulated to activity by the muscular exercise in moving about and by reflex contractions from putting food into the empty stomach. The chain of reflexes thus set up results in a call to defecation.

Valves of the Rectum.—The function of the valves of the rectum has been studied by various investigators. Bodenhamer,[100] however, denies their existence as definite valves, claiming them to be merely semilunar ridges of mucous membrane. Pennington[101] described them in detail and stated that they have definite functions, according to his experimental studies on both living and dead subjects. He found that the valves function to prevent feces from crowding down on the anus, that they equalize the pressure of the feces that accumulate in the rectum from time to time and that they facilitate defecation by giving a spiral motion to the content of the bowel. In support of his views, he cited the fact that man is the only animal possessing them and he is the only animal that defecates regularly. Irritants and foreign bodies cause them to become erect and present as a sort of ledge across the bowel, and in some cases they are directed upward, forming distinct cups or pockets, as demonstrated in plaster casts taken of them. In certain subjects they are enlarged, sometimes so much that they may interfere with normal defecation.

Other Movements of the Colon.—A fifth variety of movement takes place in the colon, which is described ordinarily as a pendulum or large swinging type of motion, and has been observed chiefly during roentgenologic studies. These movements seem to be concerned especially with the aid of absorption and take place in the transverse colon. This portion of the colon assumes a totally different position, first being in a high and in a few minutes in a lower part of the abdomen.

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100. Bodenhamer, W.: Are There Veritable Valves in the Rectum? New York M. J. **71**:1026 (June 30) 1900.

101. Pennington, J. R.: New Points in the Anatomy, Histology, and Pathology of the Rectum and Colon, Chicago M. Rec. **19**:392, 1900.

This section was described by Walsham and Overend, in 1916, by Rieder,[102] and by Currie and Henderson,[103] in 1926, who also noted gentle swaying movements in direct observations on the colon of the guinea-pig, which they thought were produced mainly by the longitudinal muscles. In addition to the type of movement studied by the aid of the roentgen rays, by abdominal windows and by direct observation, valuable contributions have been made by the observation of strips of bowel excised from the large intestine.

Alvarez commented on the sluggishness of the colon and exhibited many tracings to show the contractions of excised bits of its musculature, which reveal a very slow rate with pronounced tonus waves. From five different segments of the cecum there was little difference, the beats possessing little rhythmicity, as compared with that of the small bowel. Kolda,[104] in 1926, made similar observations on the large intestine of the cat and obtained six contractions, at the rate of six in five minutes, and these were of a similar nature to Alvarez's results. From the studies of Alvarez and Starkweather, there appears to be a downward metabolic gradient (determined by the catalase content) from the tip to the base of the cecum of rabbits and guinea-pigs. From the base the gradient is upward to the colon. They bring out a physiologic reason for this difference in that the cecum is a food reservoir which, in order to retain its contents, contracts seldom and is not influenced by happenings in the other parts of the gastro-intestinal tract. Cannon,[13] in 1911, showed that mechanical extension was the most efficient stimulus for exciting activity in the colon, just as it is for other types of smooth muscle such as that of the small bowel, ureter and bladder. Magnus,[105] in 1904, seems to have been first to record the longitudinal movements of short length strips of bowel, which has been called the Magnus method. Currie and Henderson used strips from the first part of the ascending colon of the guinea-pig and found small, rhythmic movements with a rate of about thirty-eight each minute, and at times larger contractions which they thought were the result of summation of the smaller ones. In the transverse colon, the strips beat rather irregularly with long, slow tonus waves, and in the sigmoid portions they obtained high tonus waves, but these were less frequent than those of the transverse segment.

102. Rieder, H.: Die physiologische Dickdarmbewegung beim Mensche, Fortschr. a. d. Geb. d. Röntgenstrahlen **18**:85, 1912.

103. Currie, G. C., and Henderson, V. E.: A Study of the Movements of the Large Intestine of the Guinea Pig, Am. J. Physiol. **78**:287 (Oct.) 1926.

104. Kolda, J.: Contribution a l'étude des mouvements de l'intestin isolé, Compt. rend. Soc. de biol. **95**:210, 1926.

105. Magnus, R.: Versuche am überlebenden Dünndarm von Saügethieren: II. Die Beziehungen des Darmnervensystems zur automatischen Darmbewegung, Arch. f. d. ges. Physiol. **102**: 349 (April 9) 1904.

Gross,[106] Flint,[68] Keith [107] and others noted the effect of a diet deficient in vitamins on the movements of the strips of colon of rats. Ordinarily, they beat with a rhythm of from two to three contractions each minute, but after deprivation of vitamin B, contractions were not elicited, and the result of this in vivo, they showed, was definite stasis in the intestinal tract. The latter was evidenced by dilatation of the ascending colon, by the filling of the descending colon with feces and by the presence of an increased number of ileocecal glands.

Reflexes Involving the Colonic Movements.—Many factors operate to aid in unifying and rendering the functions of the large intestine purposeful, and disturbance of or interference with any of these factors may lead to abnormal or ectopic movements. Just as with many other portions of the body, the colon is subject to reflexes, and although not many of these can be readily explained, yet a few have been studied thoroughly. Probably the most important of these is the gastrocolic or feeding reflex which has been described. Inflammatory lesions in the ileocecal region, such as appendicitis, may produce all grades of back pressure [18] up to the vomiting of large amounts of fluids and likewise intestinal injury, such as cutting and handling of the bowel, will delay the emptying time of the stomach.[11] This no doubt is a protective mechanism for the purpose of holding back food until the bowel becomes healed. Many investigators have shown that distention of the colon delays emptying of the stomach. White [108] produced intense irritation of the cecum of cats with mustard and olive oil, and also with croton oil, and obtained definite delay in the emptying of the stomach and even in vomiting. However, with a moderate or even a marked degree of irritation there was usually no effect. Smith and Miller [109] obtained increases in tonus as well as in peristaltic activity of the stomach and pylorus by irritation of the cecum or appendix with croton oil. Pearcy and Van Liere [110] distended the colons of dogs and found that during vigorous hunger contractions of the stomach the contractions ceased and complete inhibition took place. If the distention was continued, it

106. Gross, Louis: Discussion on the After Results of Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) **15**:71, 1922.

107. Keith, Arthur: Discussion on the After Results of· Colectomy (Partial and Complete) Performed for Colon Stasis, Proc. Roy. Soc. Med. (Sect. Proctol.) **15**:60, 1922.

108. White, F. W.: The Effect of Disease of the Lower Bowel on the Rate of Emptying the Stomach, Med. & Surg. **2**:618 (June-July) 1918.

109. Smith, F. M., and Miller, G. H.: The Reflex Influence of the Colon, Appendix and Gallbladder on the Stomach, Arch. Int. Med. **46**:988 (Dec.) 1930.

110. Pearcy, J. F., and Van Liere, E. J.: Reflexes from the Colon, Tr. Am. Gastro-Enterol. A., 1925, p. 135.

caused nausea, salivation and vomiting. Smith, Paul and Fowler [111] noted increases in activity of the stomach and especially of the pylorus when they injected air into the large intestine or massaged the cecum of patients with an irritable colon. They thus showed the presence of a definite reflex involving the colon and stomach. King [112] has shown that stimulation of the colon caused inhibition of the motor, secretory and absorptive functions of the small bowel. Pearcy and Van Liere also obtained cardiovascular respiratory reflexes from distention of the colon consisting of what appeared to be auricular extrasystoles and auricular flutter. Blood pressure also rose from 30 to 60 mm. of mercury and in some cases in man, from 20 to 25 mm. of mercury, remaining elevated as long as nine hours, and the subjects complained of flushed skin and free perspiration. In dogs they obtained an increased volume of the kidney and increased tonicity of the bladder.

More recently, Monroe and Emery,[113] after determining normal values, studied the emptying time of the stomach following irritation of the colon by turpentine, and their results indicated that the emptying time of the stomach was not especially influenced by irritation of the colon. However, there was no involvement of the peritoneum in their experiments, so it is possible that the difference in results of other investigators may have been due to this.

In a different type of experiments, in which the conditions were reversed, Surmont, Dubus and Tiberghien [64] applied stimuli to the prepyloric and duodenal regions of dogs and cats and noted the effect on the colon. In some cases no reaction whatever could be elicited on the large intestine, but in many of them contraction waves were recorded in the colon within one minute of the time of stimulation in the upper part of the intestinal tract. This, they explained, was due to a reflex and not to a peristaltic wave passing downward, because there was not enough time for this to take place. They thought it might be related to the gastrocolic reflex. Lyman, in 1913, in confirming Cannon's [11] view that the proximal part of the colon becomes quiet and relaxed as food nears the ileocecal valve, observed cats anesthetized with ethyl carbamate and then injected a mixture of starch and paste into the ileum near the valve. He noted that the colon a moment before was in tonic contraction, but as the material passed through the valve, the large intestine became motionless and relaxed, and as soon as the process was finished waves reappeared in the colon. He concluded that the mecha-

111. Smith, F. M.; Paul, W. D., and Fowler, W. M.: Mechanism of Epigastric Distress Associated with an Irritable Colon and Chronic Appendicitis, Arch. Int. Med. **47**:316 (Feb.) 1931.

112. King, C. E.: Studies on Intestinal Inhibitory Reflexes, Am. J. Physiol. **70**:183 (Sept.) 1924.

113. Monroe, R. T., and Emery, E. S., Jr.: The Effect of Irritation of the Colon on the Emptying Time of the Stomach, Am. J. M. Sc. **177**:389 (March) 1929.

nism was a local one because he could obtain it in the absence of nervous connections to the spinal cord, and that it was an example of reciprocal innervation of opposed muscles.

Drury, Florey and Florey,[114] in 1929, exteriorized a small segment of colon and demonstrated that when the dog was frightened and when local stimulation was applied this patch would turn pale, even when it was denervated, but it would not necessarily do so during mass movements. Even with movements in the portion, pallor was not observed. They do not explain the nature of the phenomena. White increased the tonus of the colon and, in this way, stimulated peristalsis by vigorous massage of the contents of the large intestine under the fluoroscopic screen. Incidentally, he was unable to move fecal matter by such massage. The value of exercise in the correction of constipation no doubt can be explained on the basis of the massaging action of the abdominal musculature on the intestinal tract, as noted by Soper.[115] The effect of exercise on the behavior of the colon has been reviewed in detail and studied extensively in some researches of their own by DeYoung, Rice and Steinhaus.[116] By inserting single balloons into a cecostomy opening in the colon of the dog, with the animal on a treadmill, they obtained rises in the motility and tonus of this organ. This increased activity was not coexistent with the period of exercise but started from one to three minutes later and receded in a few minutes, regardless of the duration of the exercise. They attempted to trace the origin and nature of this rise from exercise by sectioning the colon near the ileocecal valve in some instances, and in others near the anus. With the balloon between the two "cuts," no "exercise" response could be elicited, but above and below the two cuts, typical results were obtained. From this they deducted that there is a second parasympathetic inflow to the colon, probably vagal, coming in at the proximal end of the large intestine, and movements are stimulated by an unusual outflow of impulses during exercise. (The sympathetic nerves were intact in these experiments.) DeYoung, Rice and Steinhaus consider these rises in tonus and motility with exercise as similar in nature to the "mass movements" seen in man. Other factors which stimulate movements of the colon are the presence of formed fecal material in the rectosigmoid, gradual intermittent dilatation of the anal canal, the presence of food in the stomach and the act of defecation.

114. Drury, A. N.; Florey, H., and Florey, M. E.: The Vascular Reactions of the Colonic Mucosa of the Dog to Fright, J. Physiol. **68**:173 (Oct. 23) 1929.

115. Soper, H. W.: Studies of the Colon: II. The Restoration of Colonic Function, Am. J. Roentgenol. **11**:503 (June) 1924.

116. DeYoung, V. R.; Rice, H. A., and Steinhaus, A. H.: Studies in the Physiology of Exercise: VII. The Modification of Colonic Motility Induced by Exercise and Some Indications for a Nervous Mechanism, Am. J. Physiol. **99**:52 (Dec.) 1931.

Motor Tests of Function.—At present there are no known tests by which the estimation of the function of the colon may be determined with any degree of accuracy. It is true that by roentgenoscopic and other means the time required to empty the contents of the colon has been observed repeatedly, and some idea of the normal function of the large intestine can be obtained by these methods; yet individual variations are so great and so many factors, both extrinsic and intrinsic, exert their influence that these methods do not always seem to be reliable. Hertz,[44] in his observations, felt that the time required for a meal to be evacuated from the gastro-intestinal tract was about from thirty-three to forty-eight hours. He also found that the meal should reach the splenic flexure in about twenty-four hours, and this, in general, is the opinion of most roentgenologists. Kretschmer [117] believed the type of food itself to be a potent factor in the rate of passage through the intestinal tract; in general, coarse food progressed farther. The difference, he thought, was mostly in the small intestine and upper portion of the colon. Likewise, Burnett [118] stated that a badly proportioned dietary regimen was responsible for many disturbances in intestinal function, and the literature is replete with suggestions of this type. Elliott and Barclay-Smith, Schwarz, Carter,[119] Burnett and others have shown that there is a mixing of colonic contents, mostly in the right colon,[18] so that some of the fecal material may stay in the bowel as long as from three to five days, whereas some is voided the same day it is taken. This has been determined especially by the use of various colored beads, and Alvarez has shown that it may often be longer than this before a meal completely traverses the intestinal tract. By giving different colored small glass beads on three successive days, he found that most of his normal subjects passed only 75 per cent of the beads in about four days and after this it often was weeks before all were passed. After catharsis, the rate of passage was greatly increased and, following that, stool was not passed for a day or two, again emphasizing Alvarez's contention that after thorough defecation bowel movement should not be expected for a time because the gastro-intestinal tract is empty, rather than because of any astringent or constipating action by the drug. Naturally, the rates of emptying of the colon vary considerably; subjects with fast rates usually have soft, frothy and voluminous stools, possibly due to faulty digestion and absorption, and it may be that those with slower rates with well formed small stools show better digestion.

117. Kretschmer, Julian: Röntgenologischer Nachweis diätetischer Beeinflussung der Darmperistaltik, München. med. Wchnschr. **59**:2334 (Oct. 22) 1912.

118. Burnett, F. L.: Faulty Food Factors and Atonic Constipation, J. A. M. A. **83**:996 (Sept. 27) 1924.

119. Carter, L. J.: Fluoroscopic Study of the Large Bowel by the Opaque Enema: Analysis of Eight Hundred Examinations, J. Roentgenol. **2**:355, 1919; Further Report on the Study of the Colon by the Opaque Enema: Summary of One Thousand Examinations, Canad. M. A. J. **10**: 1112 (Dec.) 1920.

Function of the Appendices Epiploicae.—One of the characteristic findings by which the large intestine may be distinguished from the small intestine is the presence of the appendices epiploicae. They occur as small pouches of peritoneum in two rows, their line of origin being quite close to the anterior and posterior inferior longitudinal muscle bands, and extend from the cecum to the rectosigmoid juncture. No definite evidence of their true function is available, although many speculations have been made. W. J. Mayo [120] thought that they were capable of a wiping motion similar to the swaying movement of the small bowel, which aided in the defensive forces of the abdomen. Robinson [121] was of the opinion that they were concerned with movements of fluids in the colon, thus aiding absorption, but Harrigan [122] denied this, stating that their structure was simple and that they presented no evidence of a specialized function. It is Rankin's [123] belief that there is no doubt as to their being a part of the defensive mechanism, whether they move or not, because they so often are found sealed to a pathologic process, such as gangrenous appendicitis or diverticulitis. That these epiploic tags may get into mischief is evident from a series of observations by Hunt,[124] who described torsion of them with serious results.

ABSORPTIVE AND EXCRETORY FUNCTIONS OF THE COLON

Although it is true that disintegration, digestion and absorption of various foods take place in different parts of the intestine, according to the nature of the aliment, yet there is divergence of opinion regarding the types of material and the mechanism by which absorption takes place in the colon. The anatomy of the colon has been widely studied, with reference to its physiology. Starling, in 1926, pointed out that great differences exist in the structure of the colon in different animals, differences which depend not on the zoologic position of the animal but on the nature of its food. The colon of the carnivora is short and narrow with little if any cecum, and it has a relatively unimportant function to discharge in digestion and absorption. Proteins of meat are practically entirely absorbed by the time food reaches the ileocecal valve and the same applies to fats, so that only a small amount of these

120. Mayo, W. J.: The Principles Underlying the Surgery of the Stomach and Associated Viscera, Am. J. M. Sc. **133**:1 (Jan.) 1907.

121. Robinson, B. F.: The Transverse Colon and Its Meso-Colon in 140 Autopsies, M. Rev. **32**:348, 1895.

122. Harrigan, A. H.: Torsion and Inflammation of the Appendices Epiploicae, Ann. Surg. **66**:467 (Oct.) 1917.

123. Rankin, F. W.: Surgery of the Colon, New York, D. Appleton and Company, 1926.

124. Hunt, V. C.: Torsion of the Appendices Epiploicae, Ann. Surg. **69**:31 (Jan.) 1919.

absorbs. The chief function of the colon of carnivora is that of excretion. The colon of the herbivora is well developed, with sacculated walls, and the cecum is very large. This is necessary because their nutritious matter is enclosed in cells surrounded by cellulose walls, and these must be disintegrated so that absorption can take place, which is accomplished either by bacteria or by ferments in the vegetable cells themselves. In the horse, it seems there is a digestive fluid from the cecum which acts on foodstuffs, either in vitro or in vivo. In the cecum, under the action of many bacteria, cellulose is dissolved and cells are opened up to allow the contents to escape.

The colon of man is a compromise between the herbivorous and the carnivorous type. Draper [125] claimed that, with reference to the colon, human beings are dogs at birth because of the poorly developed right half of the colon; he further stated that the left half of the colon is of extreme age, of constant and important function and of fixed morphology, compared to the right half. He looks on the persistence of the right segment of the colon of man as the dominance of the experimental lengthening by the herbivora, and considers it ill adapted to man's needs. In support of this he studied the gross form of a number of normal colons and found many variations in size, position and appearance of the right side of the large bowel, as contrasted with the absence of variation on the left side. Even racially there are differences in the length of the colon, as Miloslavich [126] has shown, which depend on changes in environment, food, mode of living and climatic and social conditions. As far back as 1835, Schultz,[127] and in 1849, Brückner,[128] commented on the storage capacity of the cecum and its possible function in digestion, and Keith,[129] W. J. Mayo and others have brought out the fact that the large intestine really begins near the splenic flexure, the right portion, especially the cecum, being more nearly like a second stomach. The right half of the colon simulates that portion of the small bowel with which it derives a common origin. Draper [125] claimed that absorption of water is the earliest known function of the right half of the colon. He also pointed out that the stomach and colon have a common function, storage and churning. In the stomach this serves to blend the water with the

125. Draper, J. W.: Developmental Reconstruction of the Colon: Animal Researches and Clinical Report of Twenty-Nine Human Cases, Ann. Surg. **67**:567 (May) 1918.
126. Miloslavich, E. L.: Racial Studies on the Large Intestine, Am. J. Phys. Anthrop. **8**:11, 1925.
127. Schultz, C. H.: Observations and Experiments upon the Functions of the Cecum, Edinburgh M. & S. J. **44**:408, 1835; London M. & S. J. **8**:427, 1836.
128. Brückner, Carl: Die Function des menschlichen Dickdarms mit Hinblick auf die der Wirbelthiere, Rostock, Adler's Erben, 1849.
129. Keith, Arthur: The Functional Nature of the Caecum and Appendix, Brit. M. J. **2**:1599 (Dec. 7) 1912.

ingesta and in the colon to remove it. Neither stomach nor colon aids materially in digestion and each can be dispensed with. Many observers have emphasized the water-absorbing function of the colon, stating that this takes place in the cecum between the ileocecal apparatus and the cecocolic sphincter, a physiologic muscular contracture near the hepatic flexure, further aided by the high attachment of the splenic angle so that fluids all tend to gravitate toward the right portion. If fluids went beyond this point, they would interfere with the storage function of the colon. W. J. Mayo summarized this by saying, "Man eats with his jejunum and ileum, and drinks with his cecum. He prepares his food with organs originating from the foregut and absorbs his nutrition from those derived from the midgut." In the small bowel, water is absorbed in large quantities but its loss is made good by diffusion or secretion of fluid in the intestine, since contents of the bowel at the ileocecal valve are quite as fluid as at the pylorus. In the colon, absorption of water is not compensated by a secretion, according to Howell. Hay [130] stated that absorption in the colon is slower than in the small bowel because of the very nature of the mucosa of the two portions, and also because of the mucus secreted in the large intestine which tends to inhibit absorption.

Regarding absorption of other substances, such as drugs, there is more question. Goldschmidt and Dayton,[131] and Goldschmidt and Binger,[132] using various salts, made extensive studies on the mechanism of absorption from the colon. Using dogs, anesthetized with ether or paraldehyde, they ligated the lower part of the ileum, placed a tube in the cecum and washed through to the anus. They found that distilled water was readily absorbed and that it did not injure the mucosa. They also noted that the colon did not have a one-sided permeability, because sodium chloride passed in or out of the colon, depending on the usual

130. Hay, M.: The Action of Saline Cathartics, J. Anat. & Physiol. **16**:243, 391 and 568, 1881-1882; **17**:62, 222 and 405, 1883; On the Use of Concentrated Solutions of Saline Cathartics in Dropsy, Lancet **1**:678 (April 21) 1883.

131. Goldschmidt, Samuel, and Dayton, A. B.: Studies in the Mechanism of Absorption from the Intestine: I. The Colon; A Contribution to the One-Sided Permeability of the Intestinal Wall to Chlorides, Am. J. Physiol. **48**:419 (May) 1919; II. The Colon; On the Passage of Fluid in Two Directions Through the Intestinal Wall, ibid. **48**:433 (May) 1919; III. The Colon; The Osmotic Pressure Equilibrium Between the Intestinal Contents and the Blood, ibid. **48**:440 (May) 1919; IV. The Colon; The Behavior of Sodium and Magnesium Sulphate Solutions, ibid. **48**:450 (May) 1919; V. The Colon; The Effect of Sodium Sulphate upon the Absorption of Sodium Chloride when the Salts are Introduced Simultaneously into the Intestine, ibid. **48**:459 (May) 1919.

132. Goldschmidt, Samuel and Binger, Carl: Studies in the Mechanism of Absorption from the Intestine: VI. The Colon; The Influence of Calcium Salts upon the Absorption of Sodium Chloride in the Intestine, Am. J. Physiol. **48**:473 (May) 1919.

law of osmosis and the level of sodium chloride in the blood. This differed somewhat from Diena's [133] point of view, who maintained that the quantity of such substances passing into the intestines is not related to the osmotic pressure of the liquid introduced. Goldschmidt and Dayton and Goldschmidt and Binger also found that the colon behaves toward a solution of sodium sulphate like a semipermeable membrane, but with magnesium sulphate there was almost no absorption into the blood stream, and the failure of absorption of this substance they regard as of significance in catharsis.

The question of absorption of dextrose from the colon has been dealt with extensively by McNealy and Willems.[134] They reviewed the literature carefully, and their experimental work added valuable knowledge to this subject. With fasting dogs under hypnosis by barbital, they isolated the colon by ligatures at the ileocecum and rectum, and likewise a segment of the lower part of the ileum, about 50 per cent longer, to give about the same absorbing surfaces. They found marked constancy in the absorbing action of the colon, but much variation in that of the ileum; this was checked by determination of blood sugar, taken not from the peripheral blood as it was by former investigators, but from the vessels draining the loop of bowel in which the dextrose had been placed. They found no rise in blood sugar in the blood taken from the loop of colon, but a marked rise in that taken from the ileum. With tap water, they found they could recover 78.6 per cent from the loop of ileum and 57.3 per cent from the loop of colon in an hour, and with physiologic solution of sodium chloride, 62.6 and 52 per cent, respectively, was recovered. McNealy and Willems' conclusions were that there was no appreciable absorption of 5 per cent dextrose from the colon, whereas there was considerable absorption from the ileum. Tap water and physiologic solution of sodium chloride were absorbed rapidly by both ileum and colon. The fate of a dextrose enema, according to them, is as follows: It may stay in situ indefinitely; it may be expelled; its character may be changed by bacterial or other action, absorption may take place, or it may pass into the small bowel. The latter is most likely, according to them, and the success of this type of enema is due to such a process, with consequent absorption in the ileum. In some further studies the same investigators found that the presence of 0.45 per cent sodium chloride in a 2.5 per cent solution of dextrose (a physiologic solution of sodium chloride) favored absorption of the dextrose to a certain degree. With the use of sodium bicarbonate and

133. Diena, G.: Studio sperimentale sull' assorbimento da parte dell' intesti . . Arch. per le sc. med. **35**:62, 1911.

134. McNealy, R. W., and Willems, J. D.: The Absorption of Glucose from the Colon: A Preliminary Study of the Glucose Enema, Surg., Gynec. & Obst. **49**:794 (Dec.) 1929.

alcohol in a similar manner, they noted no influence on absorption of dextrose. There seems to be no doubt that fluids introduced by rectum are carried as far as the cecum. Whether this is by a reversal of peristalsis or by more mechanical pressure is debatable. Starling, in a study of a patient with a cecal fistula, calculated that 500 cc. of water passes the ileocecal valve in twenty-four hours, and about 400 cc. of this is absorbed, so he feels that the colon of man is of little significance as an organ of absorption.

A number of drugs have been studied from the standpoint of their absorption when given rectally. Hatcher and Wilbert,[135] Menninger and Heim,[136] Lesne, Hoskins,[137] Muirhead, and Barbour and Rappaport found epinephrine to be absorbed from the colon and to give the usual physiologic effect. However, Menninger and Heim found that giving the drug this way is unreliable, producing little if any effect in about half of the cases, but that whatever effect there is persists longer, hence it should be of advantage when long effect and repeated doses are required, as in Addison's disease. Levy gave digitalis rectally and found it taken into venous circulation chiefly by way of the mesenteric and portal systems. By a similar method, he gave sodium iodide, and by roentgenographic methods found it to be absorbed from the lower portion of the sigmoid; with bromides, a similar result occurred. It is commonly known that ether and other anesthetic agents are readily absorbable by rectum and produce narcosis.

Urine, without doubt, can be absorbed from the colon, and in birds and certain lower mammals this is probably at times a normal condition, because of the presence of the cloaca which acts as a common receptacle for ejection of both urine and feces. Baird, Scott and Spencer [138] showed that the entire output of urine cannot be drained into the upper part of the intestinal tract of a dog, as its absorption gives toxic symptoms that cause death in from seven to twelve days. Likewise, Cecil and Cummings,[139] after studying a case in which implantation of the ureters was made low in the colon, felt that prolonged absorption of these products occasionally produced a picture resembling chronic nephritis. However, at present, surgeons do not hesitate to

135. Hatcher, R. A., and Wilbert, M. I.: Pharmacology of Useful Drugs, Chicago, American Medical Association, 1915.

136. Menninger, W. C., and Heim, H. S.: The Rectal Administration of Epinephrin, Am. J. M. Sc. **172**:425 (Sept.) 1926.

137. Hoskins, R. G.: The Sthenic Effect of Epinephrin on Intestine, Am. J. Physiol. **29**:363 (Jan.) 1912.

138. Baird, J. S.; Scott, R. L., and Spencer, R. D.: Studies on the Transplantation of the Ureters into the Intestines, Surg., Gynec. & Obst. **24**:482 (April) 1917.

139. Cecil, A. B., and Cummings, R. S.: The Remote Effects of Absorption of Urine from the Colon: A Case of Traumatic Unilateral Uretero-Intestinal Anastomosis, J. Urol. **2**:469 (Dec.) 1918.

implant ureters into the colon, and they regard any dire results from absorption as unlikely.

Absorption of organic substances in the colon takes place to a much less marked degree than that of inorganic substances and is of considerable significance from the standpoint of the value of nutritional enemas as well as in the mechanism of digestion and absorption.

In spite of all the experiments made during the last few years, authors do not agree regarding digestion and absorption of nutritive matter by the colon. It occurs, of course, to a much larger extent in the ileum, as Reid [140] has shown, but studies on the large intestine are not so conclusive. Maestrini made colonic stomas at different levels in the colon of the rabbit and found that the total nitrogen occurred in largest amount in the first portion of the colon and diminished toward the middle of the transverse portion, and from that point to the rectum remained more or less constant. The maximal amount of soluble nitrogen was found in the ascending colon, and fats showed considerable diminution as far as the transverse colon, so that Maestrini claimed that in the rabbit nitrogenous compounds and fats at least are absorbed in the proximal portion of the colon. Reach [141] found absorption of gelatin was much greater from the large intestine when physiologic solution of sodium chloride was added, and Bernheim [142] commented on the apparent value of the nutritive enema by citing cases in which nourishment was given exclusively for as long as ten months by rectum. Eberhard [143] stated that 300 cc. of milk and two eggs could be absorbed by rectum in from one to two hours, and Mutch and Ryffel [144] found that 88 per cent of the nitrogen of peptonized milk could be utilized when given by rectum. The latter authors advised against the procedure, stating that toxic materials could be produced and absorbed in this manner, and recommended that only dextrose or saline solutions be given this way. Scheel [145] noted that milk and eggs irritated the rectum and were not absorbed, so came to conclusions similar to those of Mutch and Ryffel. Begtrup [146] tried meat and milk

140. Reid, E. W.: On Intestinal Absorption; Especially on the Absorption of Serum, Peptone, and Glucose, Phil. Tr., London, s.B **192**:211, 1900.

141. Reach, Felix: Ueber Resorption von Kohlehydraten von der Schleimhaut des Rectums, Arch. f. exper. Path. u. Pharmakol. **47**:231 (March 11) 1902.

142. Bernheim, Albert: Movements of Intestines, J. A. M. A. **36**:429 (Feb. 16) 1901.

143. Eberhard, H. M.: Nutrient Feeding per Rectum by the Drop Method, Am. J. Gastro-Enterol. **2**:5, 1912.

144. Mutch, N., and Ryffel, J. H.: The Metabolic Utility of Rectal Feeding, Brit. M. J. **1**:111 (Jan. 18) 1913.

145. Scheel, V., and Begtrup, E.: Nutrient Enemas, Ugesk. f. læger **77**:520 (April 1) 1915; abstr., J. A. M. A. **64**:1804 (May 22) 1915.

146. Begtrup, E.: Feeding by Way of the Rectum, Arch. f. Verdauungskr. **21**:400 (Nov.) 1915; abstr., J. A. M.A. **66**:1062 (April 1) 1916.

amino-acids, along with sugar solutions, and stated there was a definite increase in elimination of nitrogen, so that no doubt some nitrogen was absorbed. In general, Cornwall [147] obtained similar results and recommended nutrient enemas of amino-acids with dextrose and other fluids to maintain nitrogen balance in cases in which food cannot be given by mouth.

Carnot and Bondouy [148] studied the content of the colon of a man through a cecostomy opening and found that carbohydrates pass rapidly into the cecum in which, for the most part, they are absorbed. The presence of starch in the cecum was noted from three to six hours after ingestion, and this also was soon absorbed. Egg albumin was found at the cecum in the form of albumin and albumose, but this gradually disappeared and albumin, albumose or peptone was not seen in the stool, indicating that some absorption took place.

In this connection, Howell showed that the splitting of the protein molecule is completed by the process of putrefaction, and the list of end-products is long: peptones, proteoses, ammonia and amino-acids; also indol, skatol, phenol, phenylpropionic acid, phenylacetic acid, fatty acids, carbon dioxide, hydrogen sulphide and marsh gas. Phenol, indol and skatol, he stated, are absorbed and excreted in the urine. However, from Carnot's and Bondouy's [148] study on the absorption of fats in the colon, they could come to no definite conclusions. They found neither biliary pigment nor bile salts at the cecum, although urobilin was present. Áldor [149] found that fats were slower to absorb when given by rectum than either carbohydrates or albumins. However, it seems that the main difficulty in dealing with nutrient enemas, according to Goodman,[150] is that a nitrogen balance cannot be maintained by their use alone, due to inability of the colon to absorb or to render absorbable nitrogen-containing compounds in the enemas. From Howell's observation it seems that considerable digestion may take place in the colon, as dogs with from 80 to 83 per cent of the small bowel removed seemed to get along quite well unless excess roughage or fat was given in their diet. Starling, however, stated that little if any absorption of egg albumin or caseinogen solution takes place by rectum. In his experiments, a small amount disappeared in a considerable time, and he considered this due to bacterial action. He concluded that feeding by

147. Cornwall, E. E.: A Plan of Rectal Feeding. J. A. M. A. **70**:1451 (May 18) 1918.

148. Carnot, P., and Bondouy, H.: État de la digestion au niveau du caecum, Compt. rend. Soc. de biol. **81**:487, 1918; État de la digestion au niveau du coecum, Arch. d. mal. de l'app. digestif **10**:123, 1919.

149. Áldor, Louis: Untersuchungen über die Verdauungs- und Aufsaugungs-fähigkeit des Dickdarms, Zentralbl. f. inn. Med. **19**:161 (Feb. 19) 1898.

150. Goodman, E. H.: Diseases of the Digestive Tract and Allied Organs, the Liver, Pancreas, and Peritoneum, Progrès méd. **4**:17, 1915.

nutrient enemas is of no value and should be limited to saline solutions, water and dextrose.

Excretion.—That the physiology of the colon includes more than that of absorption and expulsion is evident from the numerous studies which have been made on its function as an excretory organ. Voit,[151] as far back as 1860, noted that in fasting dogs the amount of fecal material often exceeded the amount of food eaten, and since then many authors have noted that the excretion products of the intestinal mucosa take part in the formation of the fecal material. Peola[152] stated that in many instances the greatest quantity of feces is not made up of alimentary products, but of those of excretion from the intestine, and especially from the large bowel, although Voit stated that most of this excretion is confined to the small intestine. Voit further contended that almost all of the nitrogen content of the feces comes from intestinal secretions. Starling regarded the colon of carnivora chiefly as an excretory organ, since it played an important part in the elimination of calcium, magnesium, iron and phosphates, and he also mentioned that ulceration found in the large bowel following poisoning by mercury may be due to excretion of this drug by this route.

In his work on dogs, Draper[153] found that the right portion was relatively inactive as compared with the left portion in the excretion of various drugs and toxins. He noted that in poisoning by pilocarpine or diphtheria the mucosa of the proximal portion of the colon was bright scarlet, whereas that of the left portion remained normal. In 1929, Underhill, Peterman and Steel,[154] studying the fate of aluminum intravenously injected, found widespread elimination of the metal through the stomach and the small and large bowel. Bargen, Osterberg and Mann,[155] using dogs with colons isolated as previously described, except opening only at the cecal portion, studied the excretion of some of the heavy metals. They found that arsenic in the form of neoarsphenamine or meta-amino-para-oxyphenyl-arsenic acid, and mercury, mercurochrome and metaphen were excreted not at all or very little through

151. Voit, Fritz: Beiträge zur Frage der Secretion und Resorption im Dünndarm, Ztschr. f. Biol. **29**:325, 1892.

152. Peola, Flora: Sulla funzione emuntoria dell' intestino crasso, Gazz. d. osp. **46**:1181, 1925.

153. Draper, J. W.: Studies in Intestinal Obstruction, with a Report of Feeding Heterologous Jejunal and Ileac Cells to a Human Being, J. A. M. A. **63**:1079 (Sept. 26) 1914.

154. Underhill, F. P.; Peterman, F. I., and Steel, S. L.: Studies in the Metabolism of Aluminum: IV. The Fate of Intravenously Injected Aluminum, Am. J. Physiol. **90**:52 (Sept.) 1929.

155. Bargen, J. A.; Osterberg, A. E., and Mann, F. C.: Absorption and Excretion of Arsenic, Bismuth and Mercury: Experimental Work on the Colon, Am. J. Physiol. **89**:640 (Aug.) 1929.

the colon. Bismuth, they noted, whether given by mouth or intramuscularly, was eliminated through the large intestine. Peola commented on the serious inflammation of the intestinal mucosa and especially of the colon in uremia, and stated that toxic materials are probably eliminated by this route. He quoted a number of observers whose experiments show that under pathologic conditions, such as that in which the kidneys are impaired, urea, salts and medicinal substances may pass through the intestines. Renon and Ricket [156] found that sugar could be eliminated in the intestine in diabetes, so much so as to cause diarrhea at times. No doubt this may account for some of the attacks of diarrhea experienced by diabetic patients. Peola, in acute experiments, using isolated loops of colon, injected methylene blue (methylthionine chloride, U. S. P.) intravenously and found it to be excreted partly by the kidney and partly through the colon. After ligating segments of both small and large bowel in the cat, Taylor and Fine [157] found only a small amount of calcium was excreted through either of these portions of the bowel, most of it coming through the kidneys.

Ileocecal Valve.—A study of the physiology of the colon would not be complete without mention of the ileocecal valve or sphincter, and some of its functions. A comprehensive review of the literature will not be attempted, but merely a record of outstanding factors influencing or influenced by the large intestine. The importance of this sphincter is evidenced from the fact that certain observers have stated its proper function is just as essential to intestinal absorption as in the pylorus, and the former makes possible absorption of 95 per cent of the food before the cecum is reached. Alvarez quoted Rutherford and others as having observed in patients with cecal fistulas swaying movements associated with the to-and-fro contractions of the terminal portion of the ileum. About 4 cc. of semifluid feces came out of this sphincter in a jet every few moments; the lumen was enlarged and the circular fibers were relaxed. Viault and Jolyet [158] regard this act of the passage of excreta from the small into the large intestine as "internal defecation." Normally, this sphincter varied in tautness from the condition observed by Rutherford in which even a no. 12 French catheter could not be passed, to that observed by Short, in which he could easily insert his finger during relaxation. Macewen [159] was the first observer to be impressed with the sudden increase in activity of this sphincter after

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156. Renon and Ricket, quoted by Peola: Gazz. d. osp. **46**:1181, 1925.

157. Taylor, N. B., and Fine, A.: Excretion of Calcium Through the Intestine, Am. J. Physiol. **93**:544 (June) 1930.

158. Viault and Jolyet, quoted by Luciani: Human Physiology, London, The Macmillan Company, 1913, vol. 2, p. 364.

159. Macewen, William: The Function of the Caecum and Appendix, Lancet **2**:995 (Oct. 8) 1904.

the taking of food, which Cannon [13] has shown initiates movements in the cecum and ascending colon. Hertz and Newton also saw that filling of the proximal portion of the large intestine generally took place passively and quite slowly, and in this manner, at times, considerable pressure was exerted when the chyme was forced through the sphincter. Berlatzky [160] and Hertz [44] noted great increase in the rate of passage of contents of the ileum into the colon with the taking of food.

Ileocecal Sphincter.—Alvarez observed that the function of this structure is to prevent the reflux of foul bacteria-laden contents of the colon, when absorption is slight, into the ileum where absorption is good, and to prevent too rapid passage of feces through the last segment of the small bowel. In event of the latter, no doubt diarrhea would often occur and symptoms of true auto-intoxication, whatever they may be, might be expected. As mentioned, the ileocecal sphincter is subject to reflexes such as the gastro-ileac or feeding reflex. Hinrichsen and Ivy [161] found that stimulation of the pyloric sphincter resulted in contraction of the ileocecal structure; likewise, distention of the stomach, duodenum, ileum or colon resulted in a similar action. In a large series of experiments they found that this sphincter may contract through either extrinsic or intrinsic mechanism. They found both motor and inhibitory fibers running to it from the vagus and motor fibers alone in the splanchnic system. Contraction of the sphincter resulted also from stimulation of both the hypogastric and pelvic nerves. They concluded that this is as true a sphincter as that of the pylorus, and that it stands in the same relation to the colon and small bowel as the pyloric sphincter does to the stomach and duodenum. The angle at which the ileocecal valve enters the colon has been the subject of much discussion because of the relationship it bears to intussuception. In cases in which there is disproportion in diameter of the two segments of bowel, along with excessive mobility, there is a tendency of the ileum to invaginate into the cecum.

This sphincter is no doubt of significance pathologically, both with reference to the digestive tract and the body in general. However, definite proof of a mechanism by which any influence of this nature takes place is lacking. Incompetence of the valve with regurgitation of the contents of the colon into the ileum has been blamed for many of human ills, notably auto-intoxication, pernicious anemia, neurosis and epilepsy, yet, insufficiency of this sphincter seems to be present too often in normal individuals to lay the blame to such mechanism. Alvarez

160. Berlatzky, quoted by Luciani: Human Physiology, New York. The Macmillan Company, 1913, vol. 2, p. 366.
161. Hinrichsen, J., and Ivy, A. C.: Studies on the Ileo-Cecal Sphincter of the Dog, Am. J. Physiol. **96**:494 (Feb.) 1931.

this a swelling appeared in Petit's triangle, which was aspirated. A roentgenogram was again made and it was found that the mass had extended to the sacrum below and to the first lumbar vertebra above. The patient died on November 27.

Roentgenograms taken post mortem showed areas of destruction in the cervical and lumbar spine, nodules in the ribs and in both humeri and femurs. Roentgenograms of the skull were negative.

Fig. 19 (path. no. 46954, case of Dr. Eisenberg and Dr. Wallerstein).—Malignant paraganglioma of the suprarenal gland metastasizing to the gums, skeleton and visceral organs in a white woman, aged 55. The photomicrograph shows the large preganglionic cells and smaller neuroblasts among the more moderate-sized chromaffin cells of the paraganglionic type.

At autopsy three distinct tumor masses were found. An enormous mass was found in the lumbar region. Another elongated mass 1 inch in length which had the appearance and feeling of firm butter was found at the level of the second dorsal vertebra. The third mass was anterior to the second cervical vertebra and was similar in appearance to the second growth. The large lumbar mass was soft and fluctuant. The body of the second lumbar vertebra was entirely resorbed. The suprarenal glands were normal on gross examination. No other tumor masses

were found. All the viscera appeared normal. The tumor was composed of epithelial masses surrounded by a loose and delicate stroma. Many of the nuclei were large and had the appearance of those of a malignant tumor. At the margins the tumor resembled a typical tumor of the carotid body. In other parts of the section many small spindle cells with dense nuclei, such as occur in a neuroblastoma, were found.

Pathology.—Paragangliomas of the suprarenal gland rarely attain large size. The small tumors are solid; the larger, more often cystic and hemorrhagic. They are usually definitely encapsulated, yellowish and mottled red. The smaller tumors are surrounded by a rim of compressed suprarenal cortex.

These tumors have an alveolar structure, but the cell grouping is more regular than that of the tumors of the carotid body (fig. 2). The cells vary markedly in size, the cuboidal and polyhedral forms of moderate size predominating. In paragangliomas of the suprarenal gland there is a tendency toward syncytial formation. In the malignant forms giant, atypical ganglion and large spindle cells are found. Malignant paragangliomas are remarkable because of the size and variety of the giant cells. Eisenberg and Wallerstein have said that the greatest imaginable irregularity in the size and shape of the cells and nuclei is the most striking histologic feature.

The epithelial cells, when freshly stained with chrome salts or when fixed in Zenker's solution, show pigmented granules. After prolonged fixation in formaldehyde the cytoplasm will stain deeply with hematoxylin, a characteristic also of the cells of the normal medulla of the suprarenal gland.

ARGENTAFFIN TUMORS OR PARAGANGLIOMAS OF THE GASTRO-INTESTINAL TRACT

In 1910, Huebschamm, after studying a group of small and slowly growing tumors of the appendix and intestine, came to the conclusion that the growths developed from cells belonging to the chromaffin system. Oberndorfer had before separated these tumors from appendical carcinoma and had given them the name carcinoid. The work of Masson supported the contention of Huebschamm as to the chromaffin origin of these tumors. These tumors are now regarded as paragangliomas.

These tumors occur twice as frequently in the appendix as in the small intestine, and are relatively rare in the large bowel. Over three hundred cases of this tumor of the appendix have been reported. Over one hundred have occurred in the small intestine, and cases of these tumors in the stomach, large bowel and rectum have been recorded. Raiford recently reported twenty-nine cases from the Surgical Pathological Laboratory of Johns Hopkins Hospital. At the time this paper

was written this number had increased to thirty-five. Twenty-two of the tumors have occurred in the appendix, ten in the small intestine, two in the large bowel and one in the stomach.

As in other paragangliomas, the tumors of the gastro-intestinal tract occur usually in adults. The extreme ages in our series are 12 and 66 years. Symptoms appear earlier when the appendix is involved and the average age is less than when the tumor develops in the intestine. The symptoms of appendical carcinoids are suggestive of appendicitis, and not infrequently when an operation is performed for appendicitis a
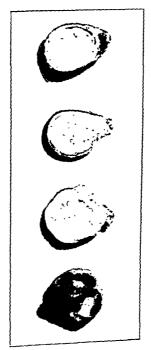
Fig. 20 (path. no. 47648).—Gross specimen of a typical argentaffin tumor situated in the end of the appendix. The lumen of the appendix is compressed but not invaded by the tumor tissue.

paraganglioma is found. When the tumor occurs in the intestine, diarrhea without melena is common. The symptoms are often due to an incomplete obstruction of the lumen of the appendix or intestine.

The majority of these growths are benign and run a slow course. About 20 per cent undergo malignant changes. Eight of the cases in our series were malignant, metastases forming in the lymph nodes of the mesentery, in the glands about the aorta and in the liver. In the malignant cases acute obstruction may develop. Argentaffin tumors of the small intestine become malignant more frequently than do those of the appendix.
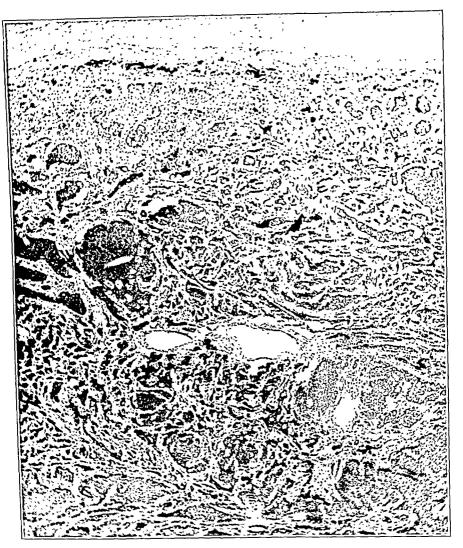
Fig. 21 (path. no. 48429).—Argentaffin tumor (carcinoid) involving the cecum in a woman, aged 46, with abdominal symptoms of two weeks' duration. The photomicrograph shows the islands of epithelial-like structures typical of all the benign paragangliomas. Among these islands and toward the lower portion of the pictures groups of small deeply staining cells arranged in rosettes are seen. The cycle of growth illustrated is from the small neuroblastic tissue to the larger masses of cells of a chromaffin nature. Metastases were present in the regional mesenteric nodes. The patient has remained well for three years following resection.

The prognosis of paragangliomas of the intestine is good. Four of eight patients in whom the lymph nodes were affected have remained well. In the fatal cases metastases have formed in the liver.

Paraganglioma of the Cecum with Involvement of Lymph Nodes.—History.—
A. B., a white woman, aged 46, was admitted to the hospital on Oct. 20, 1930,

TABLE 5.—*Data on Carcinoid or Argentaffin Tumors*

Path. No.	Sex	Age	Site	Duration	Clinical Course	Metastases
					Stomach	
40700	M	55	Stomach	10 mos.	Vague attacks of indigestion with nausea and vomiting; tenderness; laparotomy; inoperable	Liver, lymph glands
					Small Intestine	
48536	M	47	Ileum	18 mos.	Intermittent abdominal pains, intestinal obstruction; resection, 5 ft. of ileum	Mesenteric gland
36786	M	49	Duodenum	6 wks.	Pain in abdomen, vomiting; excision of small tumor nodule	None
31805	F	45	Jejunum	....	Resection, 3 cm. of small intestine	Aortic glands
G-10015	M	57	Ileum	....	Respiratory symptoms; autopsy	Liver, regional glands
G-10023	F	41	Ileum	2 days	Acute pain, nausea and vomiting; appendectomy	None
G-8875	M	62	Ileum	6 wks.	Pain in right hip and thigh following ununited fracture of neck of femur; autopsy	None
G-6739	M	50	Jejunum	1 yr.	Gastric obstruction, loss of weight; exploratory laparotomy; inoperable	None
G-4110	F	66	Ileum	7 wks.	Tenderness, umbilical hernia; rapid growth; exploratory laparotomy	None
G-3889	M	60	Ileum	2 wks.	Dyspnea and cardiac decompensation; autopsy	None
3676	M	55	Ileum	....	Symptoms of acute lobar pneumonia; autopsy	None
					Appendix	
49704	F	26	Appendix	12 hrs.	Acute gastric distress, vomiting; appendectomy performed	None
49112	F	28	Appendix	5 mos.	Symptoms of appendicitis	None
48344	F	62	Appendix	5 mos.	Abdominal pressure and distress; both tubes and ovaries removed for papillary adenocarcinoma; routine appendectomy	None
48126	M	27	Appendix	....	Abdominal distress; appendectomy	None
48124	M	60	Appendix, liver	....	Abdominal symptoms; plaques under liver, masses along root of mesentery; biopsy performed	Liver, mesenteric glands
47648	F	41	Tip	....	Indefinite pain; appendectomy	None
47522	F	16	Tip	....	Dull pain; anorexia, nausea and vomiting; tenderness; resection, cecum, terminal ileum and appendix; ileocolostomy	Cecum and ileum
47322	F	15	Tip	4 days	Pain, vomiting, nausea, tenderness; appendectomy	None
47168	F	28	Tip	....	Pain in side, abdomen and back, accompanied by nausea and vomiting; right oophorectomy and appendectomy	None
46846	F	14	Tip	4 days	Pain, nausea and vomiting; appendectomy	None

TABLE 5.—*Data on Carcinoid or Argentaffin Tumors—Continued*

Path. No.	Sex	Age	Site	Duration	Clinical Course	Metastases
					Appendix—Continued	
46754	M	28	Tip	6 days	Intermittent nausea and vomiting with acute pain; appendectomy	None
43818	F	15	Tip	3 mos.	Indefinite symptoms of pain, nausea and vomiting; tenderness; appendectomy	None
43638	F	16	Tip	6 mos.	Pain, nausea and vomiting; appendectomy	None
42135	M	15	Base	18 hrs.	Severe pain and vomiting; tenderness; appendectomy	None
38799	M	23	Tip	1 mo.	Intermittent attacks of indigestion with pain, distention, vomiting, fever; tenderness; appendectomy	None
38053	M	22	Middle	2 days	Sudden continuous pain in right flank; tenderness and subnormal temperature; appendectomy	None
37636	F	28	Middle	....	Appendectomy and suspension of uterus	None
34485	F	27	Tip	5 yrs.	Indefinite attacks of pain; severe attack day before admission; appendectomy and cholecystectomy	None
31301	F	33	Tip	....	Pain, nausea and vomiting; appendectomy for acute appendicitis	None
21703	M	30	Tip	2 yrs.	Indigestion, intermittent pain; exploratory laparotomy; appendectomy	None
15978	M	12	Middle	2 wks.	Pain, hematemesis; mass in right side, one week; tenderness; exploratory laparotomy; appendectomy	None
G- 6032	F	64	Base	....	Fall in street car; patient brought in coma; cerebral hemorrhage; autopsy	None
					Colon	
48429	F	46	Ascending colon	2 yrs.	Intermittent epigastric pain; vomiting, distention and diarrhea; resection of terminal ileum, cecum with lateral ileocolostomy	Glands of mesentery
G-10562	M	53	Sigmoid flexures	2 mos.	Nausea, epigastric distress; pain, loss of weight, anorexia; hard, nodular masses in abdomen; autopsy	Glands, liver, lungs

complaining of attacks of abdominal pain, distention and diarrhea. For several years she had been subject to attacks of dyspepsia which were variable in duration, intensity and periodicity. The present attack differed from the preceding only in its slightly greater severity. The only relevant detail in the past history of the patient was an attack of pulmonary tuberculosis twelve years before, from which she had apparently recovered entirely.

Physical Examination.—The patient was a well nourished white woman in no acute discomfort. A small mass was palpable in the right lower quadrant of the abdomen; this was about the size of a lemon, freely movable and not tender. Roentgenograms made following a barium sulphate meal showed a dilated terminal ileum but no evidence of a constriction. Following a barium enema, however, the

roentgenograms revealed a large constricting filling defect in the cecum. This was diagnosed as neoplasm, but in view of the past history of tuberculosis the possibility of an inflammatory mass was considered. An exploratory laparotomy was advised and accepted.

Operation (Nov. 6, 1930).—When the abdomen had been opened a hard and freely movable mass could be felt in the cecum. A few of the regional mesenteric glands were enlarged and hard, but in spite of this the tumor was thought to be operable. Accordingly, the operator resected the growth together with a V-shaped piece of mesentery containing the enlarged glands. A lateral anastomosis was then made, and the abdomen was closed. Some of the enlarged lymph nodes could not be removed because they were intimately related to the superior mesenteric artery.

The diagnosis was carcinoid or argentaffin tumor of the cecum with metastases to the regional mesenteric lymph glands.

Comment.—The first pathologist who examined the growth made a diagnosis of adenocarcinoma because of the numerous pseudo-alveoli in the edges of the tumor but largely because of the rarity of carcinoid tumors in the colon. The yellow color, however, is not typical of carcinoma. The microscopic arrangement of the cells, while not absolutely conclusive, is so typical that after observing a number of carcinoids one can hardly fail to identify the type even without recourse to special stains.

The gastro-intestinal history was extremely vague. As the condition extended over a number of years, it was practically impossible to ascertain the date of onset of the first relevant symptom. This suggests that the development and growth of the tumor were extremely insidious. It would be unwise to attempt the diagnosis of a carcinoid tumor from the clinical history alone, but a tumor mass characterized by an insidious onset of vague gastro-intestinal symptoms and unusual general symptoms previous to the formation of metastasis suggests a tumor of this type.

Course in Hospital.—The patient had a stormy postoperative convalescence complicated by the development of a fecal fistula on the fifteenth day after operation. This drained freely for a time and finally closed three months later. She was discharged improved and when last heard from (November, 1933, three years after operation) she was entirely well and had gained 37 pounds (16.8 Kg.).

Macroscopic Examination of Tumor.—The specimen consisted of a resected portion of bowel 6 inches (15.24 cm.) in length. In the center of this was seen an annular constricting tumor completely encircling the bowel but producing no elevation on the serosal surface. When the specimen was opened, it was found that the tumor had partially occluded the lumen. The growth had apparently originated in the submucosa but had involved the entire wall of the bowel secondarily. The mucosa was intact over the surface. The cut section was firm in consistency and yellow. Attached to the resected mesentery were several enlarged lymph glands. One of these was quite hard and when sectioned exhibited the same yellow color as the original tumor.

Microscopic Examination.—The tumor was composed of densely packed cuboidal cells arranged in strands and compact groups. These were fairly uniform in size and possessed a moderate amount of granular cytoplasm. These granules stained dark brown or black with the silver impregnation technic, identifying the tumor as one of the argentaffin type. Occasional vacuoles could be seen near the bases of the cells. The stroma was quite dense and surrounded the nests of the cells.

leaving them as discrete islands of tumor tissue. A hyperfibrosis accompanied the metastases, so that the normal structure was almost completely replaced by the tumor and its stroma.

GANGLIONEUROMAS

Virchow, in classifying tumors of the nerves, recognized the possibility of the development of a "neuroma gangliocellulare." The description of the first case of such a tumor was published in 1870. In that year Loretz reported a case, and between that date and 1901 ten cases were reported. Tumors were described in both the sympathetic and the central nervous system. Knaus has reported a case of multiple ganglioneuroma associated with Recklinghausen's disease. Beneke reported a

TABLE 6.—*Data on Ganglioneuromas*

Path. No.	Sex	Age	Site	Duration	Symptoms	Metastases
49816	M	28	Acoustic nerve	.....	Petrous portion of temporal bone removed at autopsy for routine study of ears	None
47692 Lee	F	15	Retroperitoneal, right suprarenal	1 yr.	Pain in right leg and right side of abdomen; amenorrhea	Skull
46806 Curtis	M	10	Cervical region	1 yr.	Painless mass above clavicle	None
40083	F	45	Right thigh	1 mo.	Painful, tender, aching mass; swelling and severe pain	Recurrence; dead
37512	M	4	Neck	?	Biopsy of glands of neck, 1926; enlarged and swollen	None; dead, 1927
27088 Watson	M	Adult	Midbrain	.....	Intracranial pressure; autopsy	None
21763	M	41	Cervical region	18 yrs.	Painless nodule in left side of neck	Lungs
6711	M	28	Finger	1 yr.	Nodular, hard, pulsating mass; edema of finger	None

case in which malignant changes occurred in a ganglioneuroma, in which large ganglion cells and smaller embryonic neuroblasts from which the ganglion cells probably developed were found. By 1914, Wahl was able to collect forty-seven cases of ganglioneuroma. Twenty-five of these occurred in females; in twenty-nine of the forty-seven cases the patients were less than 30 years of age, and in twenty-nine the tumor developed in the retropleural or retroperitoneal spaces.

CLINICAL FEATURES

Including the cases collected by McFarland (ninety-three) and those appearing in recent literature (Watjen, MacAuley, Alpers and Grant, Bergonzi, Jackson and Babcock, Guizzetti, Smirnow and Bischoff) together with eight in our series, the ganglioneuromas reported to date number one hundred and eleven.

Fig. 22 (path. no. 49816).—Low power photomicrograph of benign ganglioma occurring in the acoustic portion of the eighth nerve. The ganglioneuroma is indicated by the arrow and involves the nerve just before it enters the cochlea.
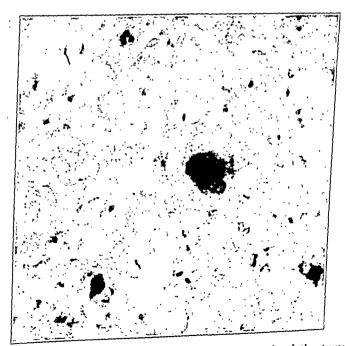
Fig. 23 (path. no. 49816).—High power photomicrograph of the tumor shown in figure 22. The large benign ganglion cells are embedded in the reticulated mass of neurogenic fibers.

These tumors are, as a rule, benign and solitary. They may be multiple and malignant, and may occur anywhere in the central or peripheral, as well as in the sympathetic, nervous system. In our cases variability in location and growth was striking. The age at which this tumor appeared varied from 4 to 45 years. Three developed in the

Fig. 24 (path. no. 47692).—Area of a malignant ganglioneuroma occurring in the retroperitoneal spaces of a girl, aged 15, with symptoms suggesting appendicitis or ureteral colic. A proliferation of cells slightly more mature than those found in typical neuroblastoma is seen.

cervical sympathetic, one in the suprarenal gland, two in the extremities, two within the skull, one in the midbrain and one on the acoustic nerve.

Three of the eight were malignant—an unusually high number. The clinical course is usually slow, marked by progressive enlargement

and eventually by symptoms of pressure. Those in the cervical region and thorax may interfere with respiration; those in the abdomen cause digestive symptoms. When occurring in the retroperitoneal spaces, the tumor may be mistaken for a malignant tumor of the kidney. Occasionally severe neuralgic pains are felt along the distribution of the nerves encroached upon. When benign, the mass is freely movable and not tender. In one case in our series the growth was extremely small.
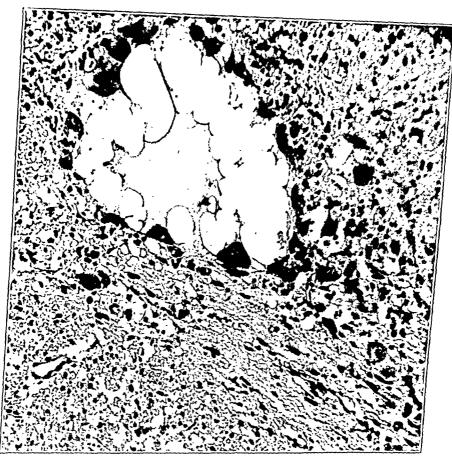
Fig. 25 (path. no. 47692).—Section from the tumor shown in figure 24. Ganglionic and adult chromaffin cells are seen embedded in a neurogenic stroma.

It developed on the auditory nerve. Because of being so rare, two of the three cases of a malignant tumor will be discussed briefly. The third case has been reported by Lewis and Hart.

A Retroperitoneal Malignant Ganglioneuroma.—A white girl, aged 15, had complained for over a year of recurrent, severe, cramplike pains in her legs. These were more severe on the right side below the knee in the muscles of the calf. Similar pains had been experienced six or seven years before. A few months before examination abdominal pain was noted. No definite diagnosis was made at that time.

When the patient was admitted to the hospital a mass could be palpated in the region of the right kidney. The right knee jerk was absent. The white blood count was 8,200, with a normal differential count. Pyelographic studies of the kidneys showed no marked deformity. The calices of the right kidney were slightly blunted, and the renal pelvis on that side seemed dilated. The right ureter was also thought to be somewhat dilated.

An operation was performed on Feb. 9, 1932. The appendix was removed through a right rectus incision and a retroperitoneal tumor palpated.

An incision was made that exposed the right kidney. A large tumor was found which extended from the right suprarenal gland, behind the ureter, down to the brim of the pelvis. The growth, which was hard and encapsulated, was removed.

Fig. 26 (path. no. 37512).—A benign ganglioneuroma arising in a cervical sympathetic in a child, aged 4, which terminated fatally. The roentgenogram shows a mass invading the mediastinum and compressing the lung.

The patient returned home on March 1. She was seen in January, 1933. At this time metastases had formed in the left parietal region. The mass was about 2 inches (5 cm.) in diameter. Her legs were atrophied. Occasional fecal incontinence was noted; amenorrhea had developed. The patient was bed-ridden. The tumor had the shape of an oyster. One hemorrhagic area the size of a marble was found; the remainder of the growth was firm and encapsulated. The cut surface was grayish-white with yellow flecks.

On microscopic examination two definite masses were found. In one of these stroma predominated. The stroma was formed of coarse fibers arranged in bundles, and a finer reticulated substance, which on cross-section looked like a normal nerve. In the stroma were embedded many large ganglion cells with a single nucleus, and small clumps of cells arranged in a syncytium with a cytoplasm which

stained deeply with hematoxylin. This tissue resembled somewhat normal medulla of the suprarenal gland.

The other portion of the tumor mass was very vascular and was formed of small cells, seemingly tightly packed together, with dense nuclei. The cells resembled those seen in typical neuroblastomas. Many were, however, larger with spindle or pear-shaped forms. Histologically, the tissues of the ganglioneuroma, paraganglioma and neuroblastoma were combined in this growth.
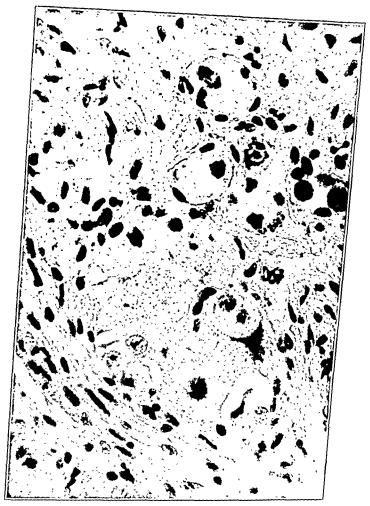
Fig. 27 (path. no. 37512).—Photomicrograph showing large ganglion cells and neurogenic stroma occurring in the tumor illustrated in figure 26.

Malignant Ganglioneuroma Occurring in the Right Popliteal Fossa.—A Negress, aged 18, had had a painful, aching sensation in the right calf for three months. When the patient was recumbent the pain was relieved. Preceding this by two years was an ailment which the patient described as a neuritis in both legs. At this time there also were noted a swelling of both legs and photophobia. The exact nature of the illness could not be determined. She attributed the pain in the right leg, complained of on admission, to a fall the year before. A definite lesion in the region of the right calf was discovered a month before.

On the posterior surface of the right thigh, about 4 cm. above the popliteal space, was a firm, tender mass which involved the soft tissues. It measured 20 by 20 by 8 cm. Its lateral and upper margins merged with and infiltrated surrounding structures. Below the popliteal space in the right calf a hard, cordlike swelling, 2 inches in length, which was extremely tender, could be palpated.

The tumor was explored on Oct. 6, 1926. It was vascular and contained mucoid tissue among the vascular areas. On October 15, the mass was excised from the thigh. The patient was admitted to another hospital in November, 1930, and an operation was performed for a recurrent tumor in the region of the right hip. The patient died on November 12, shortly after the second operation. Permission for autopsy could not be obtained.

The gross specimen measured 12 by 10 by 4 cm. It seemed encapsulated. The surface was white; the cut surface seemed fibrous, but scattered throughout were hemorrhagic and yellow areas.

The tumor varied considerably when examined microscopically. The greater portion had a hyalinized, fibrous appearance, but contained many vascular areas. In the hyalinized areas were accumulations of small spindle cells, forming a reticulum, and large spindle cells such as are found in the sarcomas arising from nerve sheaths. At the center of many such masses were cellular, fibrous areas, in which were embedded giant cells and an occasional ganglion cell. The tumor appeared to be a mixture of a benign ganglioneuroma and a sarcoma of the nerve sheath.

COMMENT

The three types of tumors which have been discussed develop from cells which wander out from the neural crest during embryonic life. The undifferentiated cell may give rise to the neuroblastoma, and as differentiation proceeds the more adult types of paraganglioma and ganglioneuroma may develop. The occurrence of all these types of tissue in the same tumor indicates a common origin, different degrees of differentiation accounting for the occurrence of the more adult type of tissue. Recently Joergensen has reported a case of hypertension associated with a retroperitoneal ganglioneuroma. Softening in the brain and spinal cord was also noted in this patient. In discussing this case he stated, "that paraganglioma has been found associated with hypertension without other discoverable etiologic factors. Some paragangliomas are composed of epinephrine-bearing tissue, while ganglioneuromas do not contain such elements." One may conclude, therefore, "that in spite of the origin of these two tumors from the common, primitive type of cell, when hypertension is associated with ganglioneuroma it is merely incidental. It is believed that the hypertension in this case can best be explained on the basis of the renal and generalized vascular changes."

No other ganglioneuromas have been reported in which hypertension was a part of the clinical picture.

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CONGENITAL CARTILAGINOUS RESTS IN THE NECK

WARREN B. MATTHEWS, M.D.

CHICAGO

Largely as a result of the historic work of Rathke [1] in 1825 on the development of structures of the head and neck from the embryonic branchial system, many hitherto unexplained anomalies of this region of the body have been better understood. Rathke noticed the similarity of the piscine gill system to the embryonic cervical structures of man, the pig, horse and chick. Other investigators followed Rathke and in rapid succession correctly related the embryonic to the normal postnatal anatomy. That congenital anomalies of the face and neck were soon interpreted as the effects of early embryonic maldevelopment is apparent. Heusinger,[2] for example, in 1864 analyzed forty-six cases of cervical and facial malformations and was well aware of their origin.

The most common defect of the branchial system in the neck of man is the lateral cervical cyst or fistula. Among the rarer defects is the presence of cartilaginous remains, or "rests," an example of which is presented in the following paragraphs.

REPORT OF A CASE

History.—A. M. B. H., a 6 year old girl, of Caucasion extraction, was brought to the clinic because of wryneck. The family history was not significant. The birth of the child had been effected by forceps delivery after a long, hard labor. She had been bottle-fed. She had always seemed healthy except for the aforementioned deformity.

When she was 3 weeks old, her mother noticed that she slept with her face turned to the left, and that a lump the size of a hen's egg was present in the right side of the neck between the right ear and the sternoclavicular junction. This lump was treated for one year by a masseuse, and during this time it gradually receded until only a very small, hard nodule remained. This persisted. The condition of wryneck seemed to the mother to have been worse during the past three years than at first.

Physical Examination.—The child was well nourished and apparently normal except for the torticollis. The left side of the head (eye, chin and ear) was held higher than the right side, and the chin pointed to the left. The right sternocleidomastoid muscle was shortened and very hard and stood out like a fibrous

1. Rathke: Isis von Oken, 1828; cited by Nieden and Asbeck.[3]

2. Heusinger: Hals-Kiemen-Fisteln von noch nicht beobachteter Form, Virchows Arch. f. path. Anat. **29**:358, 1864; **33**:177, 1865.

band. The left corresponding muscle was normal except for slight hypertrophy. Beneath the skin overlying the anterior border of the right sternocleidomastoid muscle, at a point about midway between its two ends, was a hard, movable, painless, button-like structure about 5 mm. in diameter (fig. 1). The overlying skin was normal.

Fig. 1.—Preoperative appearance of the cartilaginous rest on the right side of the neck.

Laboratory Findings.—The results of a blood count and of urinalysis were normal. The Wassermann and Kahn tests were negative. An x-ray picture (Nov. 3, 1931) showed (1) a lack of normal development of the right half of the body of the first cervical vertebra (a congenital or an acquired defect) and (2) nonfusion of the two halves of the second thoracic vertebra with absence of its posterior spinous process.

Operations.—On Nov. 4, 1931, Dr. Edward L. Compere performed a tenotomy of the right sternocleidomastoid muscle and removed a small piece of the muscle for histologic study. It proved to be only dense fibrous tissue with no muscle fibers present.

On Nov. 30, 1931, Dr. Compere removed the button-like nodule from the right side of the neck. There were no adhesions to the underlying muscle or to any other nearby structure. Grossly, it was bluish white and of uniform, hard consistency, 5 mm. in diameter and 2 mm. thick. It had the appearance of cartilage.
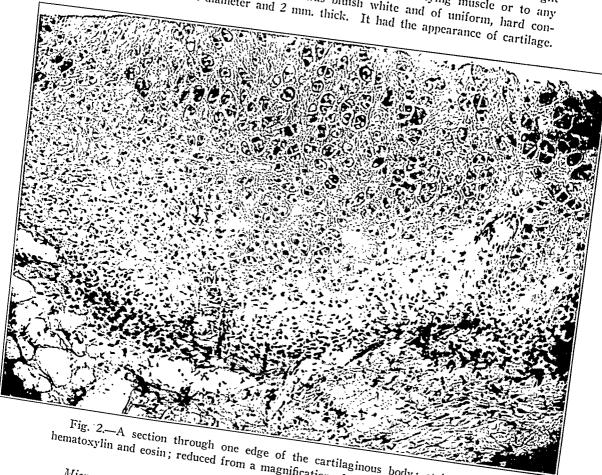
Fig. 2.—A section through one edge of the cartilaginous body; stained with hematoxylin and eosin; reduced from a magnification of × 140.

Microscopic Examination.—Sections made transversely through the specimen and stained with hematoxylin and eosin were found to be composed principally of diffusely arranged cartilage cells (fig. 2). The cell nests were irregular in outline, varying in shape from round to oval or fusiform. Most of them contained only one cell nucleus. A widely spaced intracellular portion was quite granular and seemed to have a thin framework. The more mature cells were in the more central portion of the sections, while peripherally the nuclei had more of a fibroblastic appearance. Fibrous connective tissue surrounded the cartilage and in at least one area invaded it as though through an indentation.

From the foregoing study the diagnosis of hyaline cartilage was made. However, after a search was made for elastin by Dr. P. A. Delaney of the depart-

ment of pathology (by staining with phosphotungstic acid and hematoxylin), the diagnosis was of necessity changed to elastic cartilage. In the hyaline matrix surrounding the lacunae were found many branching fibrils of elastin, interlacing like so many pieces of straw (fig. 3).

The question might be raised as to whether or not this cartilage developed as a result of the birth injury that apparently had caused a large hematoma in the right sternocleidomastoid muscle and led finally to its fibrous degeneration. Because of the nature of the cartilage, and
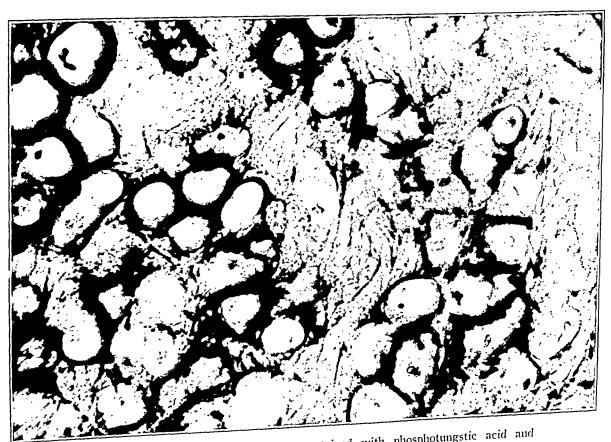
Fig. 3.—A section of the cartilage stained with phosphotungstic acid and hematoxylin; reduced from a magnification of × 700. Sections stained by Weigert's method presented the same picture. The fibers of elastin are clearly visible.

because it was completely detached from the underlying scarred muscle, I feel that this was not the case. This cartilage was much more probably a congenital remnant from the embryonic branchial system.

Of additional interest is the occurrence of the anomalous malformation of the second thoracic vertebra, which is in accordance with the common observation that maldevelopment of the branchial system is often associated with other congenital defects.

INCIDENCE

The first two cases reported were described by Heusinger [2] in 1864. Since that time reports of between seventy and eighty cases have appeared in the literature, according to a careful recent review made by Nieden and Asbeck [3] (1931). Because in several cases among this number operation was not performed or tissue removed surgically was not adequately studied histologically, the precise number is inexact. It is certain, however, that this finding is very infrequent. By far the majority of instances have been reported by European writers, and very few by American authors. Nieden and Asbeck believe that cartilaginous growths in the neck were observed by the early Greeks—that it must have been such observations that led Greek sculptors to adorn images of satyrs with horns arising just beneath the ears.

PATHOLOGIC ANATOMY

These symptomless cartilaginous tumors have been found at a typical site: between the hyoid bone, above, and the sternoclavicular junction, below; they always lie over the sternocleidomastoid muscle, usually near its anterior edge. In general, they have been found in the same locations as those where lateral cervical fistulas commonly open.

In size, these tumors vary widely between nodules the size of a millet seed and those the size of a pigeon's egg. In some instances, the nodule, if large, has hung down in a pedunculated pouch of skin. There is no typical shape; some are button-like or coinlike, and others are roughly cylindric or oval. A diagnostic feature is their hard consistency. They are not attached to the overlying normal skin and seldom to the underlying muscle, though nearly always rather firmly united with the superficial fascia of the neck. Blood vessels and nerves have been found in association with these pieces of cartilage. No mention has ever been made suggesting their attachment to thyroid or hyoid cartilage. In a fair number of the cases reported the cartilage has been found symmetrically bilateral. A few of the cartilage bodies were found in the walls of lateral cervical fistulas.

In all of the reports, save one which described elastic cartilage, the tissue was stated to be fibrocartilage. Many of the reports were made before the current distinction between elastic and fibrocartilage was so universally adopted. Perhaps some of these cases might now be classified as instances of elastic cartilage. The one case of elastic cartilage was described by Nieden and Asbeck, who made several hundred serial

3. Nieden, H., and Asbeck, C.: Kongenitale Knorpelreste am Halse und ihre Beziehung zu den seitlichen Halsfisteln, Beitr. z. klin. Chir. **153**:47, 1931 (literature).

sections and a wax model of their specimen. By this detailed examination they demonstrated two epithelial inclusions in the form of small cysts between the cartilaginous bars—supposedly pinched-off portions of branchial clefts.

There is in the literature *no* suggestion of malignant changes in these cartilaginous remnants.

PATHOGENESIS

In all the reports the authors have assumed that the cartilage originated as an isolated segment of a branchial arch. In this belief they have followed the teachings of the embryologists who interpret lateral cervical fistulas as being due to the persistence of branchial clefts. A great deal of discussion has taken place as to which one of the branchial clefts remains as a lateral cervical fistula, and which arch persists as an anomalous piece of cartilage. Nieden and Asbeck suggest that one might settle the question by following up the nerve supply to the fistula or cartilaginous body, since the derivatives of each arch and cleft have constant and characteristic innervations.

Hyaline cartilage occurs in the adult in the nose, larynx, trachea and bronchi. Elastic cartilage is found in the external ear, in the walls of the external auditory canal and eustachian tube, in the epiglottis, and in the corniculate and cuneiform cartilages. To the construction of these parts all the first five branchial arches contribute. Fibrocartilage forms the interarticular cartilages of the lower jaws.

Wenglowski,[4] in 1907, challenged the branchial origin of lateral cervical fistulas and pouches and of any associated anomalous structure. This author spent most of his time for several years collecting from numerous obstetric and gynecologic services throughout Russia seventy-eight human embryos, measuring from 2 to 49 mm. Five years were spent in making serial sections and wax models of these specimens. In addition, he carefully studied many cases of cervical cyst and fistula in children and adults. As one of the conclusions of this laborious and conscientious work he postulated that cysts and sinuses occurring along the mesial border of the sternocleidomastoid muscle, ranging from the hyoid bone to the suprasternal notch, are vestigial remains of the thymicopharyngeal duct. No embryonic remnant appearing in the neck below the hyoid bone can originate from the branchial system, according to Wenglowski. His work is discussed in some detail in a recent paper by H. W. Meyer[5] (1932). Many lateral cervical fistulas which

4. Wenglowski, R.: Ueber die Halsfisteln und Cysten, Arch. f. klin. Chir. **100**:789, 1913.

5. Meyer, H. W.: Congenital Cysts and Fistulae of the Neck, Ann. Surg. **95**: 1 and 226, 1932.

are patent throughout, and which open externally at the site just indicated, follow just the course taken by the thymic canal. This canal originates from the third pharyngeal pouch.

Wenglowski did not specifically mention cartilaginous remains in his discussion, nor is there an example included in the list of anomalies that he collected. Because these cartilaginous remains sometimes exist in the walls of, or in relation to, lateral cervical fistulas or cysts, one naturally supposes that these structures have a common origin. Therefore, one must conclude either that all the authors who have reported cases of cartilaginous remains in the neck have been in error when they have attributed them to a branchial origin or that these bodies have no embryonic connection with the lateral cervical fistulas with which they may be so intimately related.

SUMMARY

1. An instance is described in which a particle of elastic cartilage was found in the side of the neck of a 6 year old child. I think that this cartilage originated as a remnant of a branchial arch.

2. A brief review of the incidence, pathologic anatomy and pathogenesis of cartilaginous rests in the neck, as described in the literature, is presented.

EWING'S TUMOR (PRIMARY INTRACORTICAL AND SUBPERIOSTEAL LYMPHANGIO-ENDOTHELIOMA)

REPORT OF A CASE

DOMINIC A. DE SANTO, M.D.

Assistant Pathologist, Bellevue Hospital

Instructor in the Department of Medicine, College of Physicians and Surgeons

NEW YORK

Whoever studies the subject of endothelioma of the bones and endothelial tumors in general cannot fail to be struck by the great confusion in terminology and classification which exists in this field. Unfortunately, the group of the endotheliomas has become a conglomerate composed of many tumors of unusual appearance and histology. Since the morphology of endothelial tumors is, in general, far less distinctive than is that of epithelial tumors, it is not unnatural that the pathologist confronted with microscopic sections of an unusual tumor which resembles neither carcinoma nor sarcoma should choose the middle ground and make a diagnosis of endothelioma.

Although Ewing [1] was not the first to describe endothelial tumors of bone, he was the first to present a large series of cases, and, what is even more important, it was he who separated these growths into a fairly distinct clinical and roentgenologic group. Previously, the literature on the subject had consisted of reports of a heterogeny of diversified tumors some of which were undoubtedly metastatic, since few of the studies were based on autopsy. Not unlikely, a great deal of misinformation crept into the literature which still is misleading. For example, the conclusion of Howard and Crile,[2] who reviewed the literature up to 1902 and found that endotheliomas occurred in persons whose ages averaged 60 years (except in the three cases in their own series), is at great variance with that of Geschickter and Copeland,[3] who found that 95 per cent of a series of 65 endotheliomas occurred in persons

1. Ewing, James: (a) Diffuse Endothelioma of Bone, Proc. New York Path. Soc. **21**:17, 1921; (b) Further Report on Endothelial Myeloma of Bone, ibid. **24**:19, 1924.

2. Howard, W. T., and Crile, G. W.: A Contribution to the Knowledge of Endothelioma and Perithelioma of Bone, Ann. Surg. **42**:358, 1905.

3. Geschickter, C. F., and Copeland, M. M.: (a) Tumors of Bone, New York, American Journal of Cancer, 1931, p. 379; (b) Ewing's Sarcoma: Small Round Cell Sarcoma of Bone, Arch. Surg. **20**:246 (July) 1930.

under 25. Obviously, the older cases represented a condition different from the present conception of Ewing's tumor—probably metastases to the bones.

The disease named after Ewing [1a] was reported by him in 1921 as an example of bone tumor occurring in the distal end of the radius of a girl aged 14. Its histologic and gross appearance differed so markedly from that of the usual osteogenic sarcomas that he felt the necessity of a separate grouping. Subsequently, Ewing [1b] collected seven instances of this tumor and summarized his findings about as follows:

1. The tumor occurs in young persons from 14 to 19 years of age.

2. The bones affected are the tibia, ulna, ischium, parietal bones and scapula.

3. The tumors grow slowly, several months usually elapsing before they attract attention. They are often painful and tender.

4. The roentgenogram is characteristic: A large portion or the whole of the shaft is involved, and the ends are usually spared. Unlike osteogenic sarcoma, the tumor produces slight widening of the shaft, but with a gradual fading of osseous structure and absence of production of bone.

5. The tumors are radiosensitive. This is probably the most important single reason for their separate grouping.

Since the original descriptions, numerous large series of cases have been reported, notably those of Connor,[4] of Kolodny,[5] who studied the material of the Bone Sarcoma Registry, and of Geschickter and Copeland.[3] The results of the latter two studies differ from the conclusions of Ewing, which were supported by Connor, in at least one important conclusion, namely that *absence of production of bone is not a characteristic feature.* Many of their specimens showed production of bone to be as abundant as that encountered in osteogenic sarcoma, and this was true in the case to be reported. Indeed the majority showed osseous formation either parallel to or at right angles to the shaft. To regard Ewing's tumor as a primary osteolytic tumor of the medullary cavity, as is often done, is erroneous and has been responsible for many mistakes in roentgenologic diagnosis.

As an example, a recent paper reports the case of a 62 year old man with rapidly developing cachexia and a tumor involving the upper end of the humerus, the glenoid fossa and the entire scapula. Pathologic fracture of the humerus occurred. The roentgenogram of the humerus showed marked destruction of bone at the anatomic neck. The cortex was expanded. The glenoid presented a moth-eaten appearance. Shortly before death hematuria developed. The patient died of a traumatic fracture of the femur. Areas of the tumor were characterized by a

4. Connor, C. L.: Endothelial Myeloma, Ewing, Arch. Surg. **12**:789 (April) 1926.

5. Kolodny, A.: Bone Sarcoma, Surg., Gynec. & Obst. **44**:126, 1927.

solid growth of tumor cells of irregular size and shape, many being gigantic forms with vesicular nuclei and prominent nucleoli. This case, in which the diagnosis was probably made on roentgenologic findings, violates every clinical and pathologic criterion of Ewing's tumor; namely, the age of the patient; the location, with involvement of the cavity of the joint; the occurrence of pathologic fracture; the rapid cachexia, and the histologic appearance of irregularity in the size and shape of the cells.

Again, some of the published reports in the French literature, in which a great deal is being written about Ewing's tumor, describe rarefying tumors of the medullary cavity and show photomicrographs of large clear polyhedral cell tumors indistinguishable from hypernephroma. The diagnosis of Ewing's tumor is apparently being made when it is not justified. It is a rare disease comprising from 7.5 per cent to 15 per cent of all tumors of the bones. Hence, it falls to the lot of few surgeons and pathologists to see more than an occasional case in a lifetime.

NATURE OF EWING'S TUMOR

The uncertainty which surrounds the origin and nature of Ewing's tumor is expressed by the great variety of names by which it is known. "Diffuse endothelioma," "endotheliomyeloma" (Ewing), "Ewing's sarcoma" and "reticular sarcoma of the bone marrow" are but a few. Even the primary site of its appearance is a subject for controversy. Connor[4] placed it in the marrow cavity, and Ewing[1b] himself once leaned to this view. Kolodny[5] believes in an origin from multicentric foci in the medulla and cortex which soon coalesce. Geschickter and Copeland,[3] whose studies are more recent and supported by more roentgenologic evidence, believe in a primary subperiosteal or intracortical origin with secondary and minimal medullary invasion. This is in strict though not absolute contradiction to the original views of Ewing,[1b] who chose the name endotheliomyeloma in order to indicate either a medullary origin or a preponderance of medullary involvement. The pendulum appears to have swung to the opposite extreme.

The following case is reported because it is undoubtedly an example of Ewing's tumor and appears to establish the origin of the disease.

REPORT OF CASE

History.—J. V., a Puerto Rican boy, aged 5 years, had been a normal infant born at full term. The family history showed no evidence of syphilis. He had had the usual diseases of childhood, measles, diphtheria and chickenpox during his fourth year, and tonsillectomy had been performed seven months before his admission to the hospital. Eight months before his admission, the left leg began to swell and caused pain when he walked. At that time he entered another institution

where he remained for a short time. Roentgenologic studies were made, and the diagnosis was osteomyelitis. The family refused to permit operation and withdrew the child from the hospital. He was admitted to the children's surgical service at Bellevue Hospital on Jan. 21, 1932.

Physical Examination.—The patient was slightly undernourished. The left tibia showed a smooth, diffuse, spindle-shaped enlargement of the entire shaft, which stretched the overlying skin. The leg was not tender, and the overlying soft tissues did not appear inflamed.

The submaxillary, tonsillar, inguinal and cervical nodes were slightly enlarged. Physical examination otherwise gave negative results. No stigmas of syphilis or rickets were present.
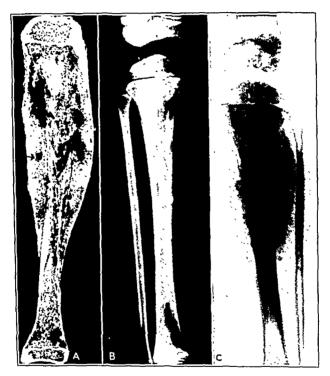
Fig. 1.—*A*, photograph of the specimen. The arrow indicates a hemorrhagic cyst. *B*, roentgenogram taken in August, 1931, shortly after the onset of pain. There are periosteal elevation on the lateral surface of the tibia and new bone formation. Note also the increased density of the lateral half of the proximal portion of the tibia, indicative of new bone formation in the medulla. The roentgenologic diagnosis was chronic osteomyelitis. (Reduced from an 8 by 10 inch film.) *C*, roentgenogram taken on Feb. 15, 1932, showing extensive formation of bone beneath the periosteum and at right angles to the shaft, and also increased density of the medullary cavity. The epiphysis is uninvolved. The diagnosis was osteogenic sarcoma. (Reduced from a 12 by 14 inch film.)

Laboratory Findings.—Roentgenograms of the long bones and of the lungs were made. The roentgenogram of the left tibia showed separation of the periosteum with evidence of formation of new bone springing radially in both directions. The upper end of the shaft showed several areas of osseous rarefaction. The lungs,

the bony thorax and the long bones contained no metastatic foci. Several roent-
genograms were taken without leading to a substantial change in the diagnosis,
which was "osteogenic sarcoma." This diagnosis was made despite the failure of
the tumor to involve the epiphyses and was based on the predominance of produc-
tion of bone.

The original roentgenograms taken eight months before the patient's admission
were consulted. These showed the periosteum of the upper third of the left tibia
to be raised on both the inner and the outer aspects. There was production of
new bone beneath the raised periosteum at right angles to the long axis of the
bone together with irregular production of bone in the upper end of the shaft.
The process in no instance extended beyond the epiphyseal line.

Course.—The patient received radiation therapy on January 27. Biopsy was
performed on February 5. Following the report on the biopsy, amputation of the
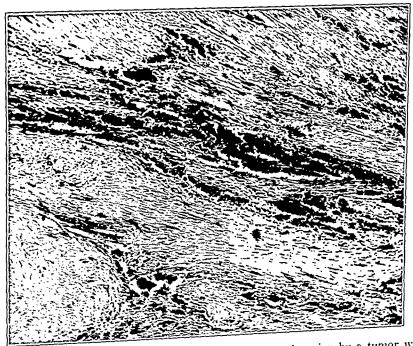
Fig. 2.—Photomicrograph of the periosteum showing invasion by a tumor which
extends along slitlike lymphatic spaces. Hematoxylin-eosin stain; × 100.

middle part of the thigh was performed on February 15 by Dr. Beekman and was
followed by a course of erysipelas and prodigiosus toxins (Coley) administered with
slight interruptions until the date of discharge, which was May 15, 1932.

The patient is alive and well at the time of writing, with no clinical or roent-
genologic evidence of metastases.

Gross Pathologic Study.—The description is concerned with the tibia alone.
The specimen was 23 cm. in length and 5 cm. in maximum width, which was at
the midshaft. The periosteum of both the inner and the outer surfaces was raised
from the cortex for an average distance of 1 cm. Beneath the periosteum was a
fairly dense deposition of bone arranged at right angles to both the periosteum
and the shaft. The new bone varied considerably in consistency, being dense in
some places and soft and spongy in others. The process stopped sharply at the
proximal epiphysis and ended distally about 5 cm. from the lower epiphyseal junc-

tion. In the middle of the shaft on the inner aspect directly in the region of sub-periosteal formation of new bone was located a cyst, approximately 2 by 1 cm. in size, which was bridged by slender strands and filled with chocolate-colored material.

The cortical bone was lamellated, and instead of having a compact structure it was composed of a series of parallel, splinter-like units of bone. In the mid-shaft, the cortex was widened, encroaching on the marrow cavity. The medullary cavity of the entire shaft was composed of spongy bone of varying degrees of density, and only in the uninvolved distal portion was there any marrow. In general, the dense bone was at the proximal end of the shaft. The epiphysis and the epiphyseal line appeared natural.

Microscopic Examination.—Sections were removed in the following manner: (1) a transverse block of bone from periosteum to periosteum including the cortical
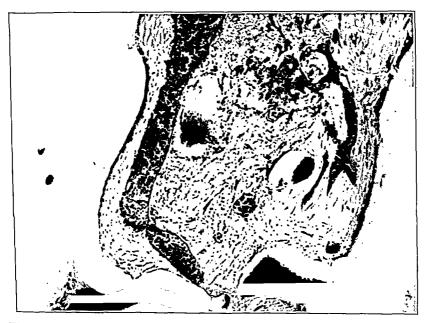
Fig. 3.—Photomicrograph of the cortical bone. The lamellae are separated, and the haversian canals are widened. Note the dilated perivascular lymphatics whence the neoplasm presumably arises. Hematoxylin-eosin stain; $\times$ 100.

bone; (2) a transverse block of bone from periosteum to periosteum not including the cortical bone; (3) a block of bone through the proximal epiphyseal junction, and (4) a block of bone through the cystic area.

These were fixed in 10 per cent formaldehyde, decalcified in 10 per cent nitric acid, embedded in paraffin and stained by routine methods. In addition, the Giemsa and van Gieson stains and a Pianese stain for colloid were used.

In the microscopic report, for convenience of description the four zones in the tumor will be considered: (1) the periosteum and surrounding muscular tissues; (2) the subperiosteal zone of new bone formation; (3) the cortical bone, and (4) the medullary cavity.

Because of technical difficulties incident to the cutting of sections of bone, most microscopic studies are based on examination of small pieces of tissue, often dis-

closing an atypical histologic picture. In this case an attempt was made to study the topography as well as the histology of the tumor.

Periosteum: The periosteum was studied by means of transverse and tangential sections. It appeared as a slender band of dense collagen fibers, surrounded in areas by striated muscle. The periosteum at the proximal end of the shaft appeared thickened and was occupied by a growth presenting the following characteristics: The cell was approximately the size of a lymphocyte with a round nucleus containing scattered chromatin particles. The nucleus was characteristically round but in rare instances vesicular and elongated. The cytoplasm was clear; it was usually indistinct, but when visible was polyhedral. The cells were uniform in size and shape. In the periosteum the cells were arranged in compact masses, strands and branching columns and invariably were found lying in slitlike tissue spaces lined by endothelium.
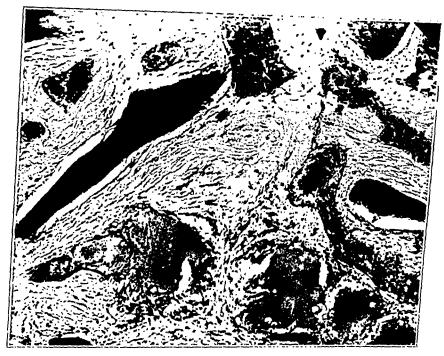
Fig. 4.—Photomicrograph through a block of subperiosteal tissue. Note the dilated perivascular lymphatics, the laying down of new connective tissue and the spicules of newly formed bone. Hematoxylin-eosin stain; × 100.

Subperiosteal Zone: In this zone two separate processes were present, one of formation of bone, and the other of tumorous infiltration. The zone was occupied by a meshwork of osteophytes, usually arranged at right angles to the long axis of the bone. These osteophytes represented new spicules of bone and could be seen in every stage of formation by the agglomeration of osteoblasts. Occasionally chondroblasts with acidophilic nuclei formed a peripheral zone in the spicule.

The osteophytes were embedded in a stroma of vascular loose fibrous tissue. Large distended blood vessels were present in this stroma lying in the same direction as the newly formed bony trabeculae.

The tumor was represented by a structure consisting of a multitude of elongated, vesicular spaces lined by several rows of cells identical with the tumor cells described and containing compact masses of the cells lying free in the lumens.

The spaces appeared to intercommunicate freely, giving the whole a loose reticular aspect. As the tumor was traced inward and toward the cortex it assumed a more cystic character and was composed chiefly of a multitude of oval spaces lined by a single or a double row of tumor cells and containing fluid that had unquestionably the staining properties of lymph. There was a diffuse growth of small tumor cells, but the cystic nature of the growth predominated. The dilated lymph spaces (which they undoubtedly were) often lay adjacent to osteophytes but were in no way directly transformed into osseous tissue. Often, papillary infoldings lined by endothelium could be seen projecting into them. Often the coalescence of numerous such spaces produced a multilocular cyst.
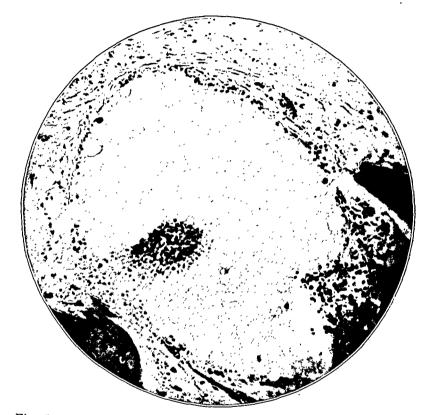
Fig. 5.—Higher magnification of dilated subperiosteal lymphatics. Note the lining endothelium, the papillary ingrowth of endothelial cells and the fluid lymph. Hematoxylin-eosin stain; × 500.

Elsewhere the lymphatic spaces were seen to contain red blood cells, and in a few instances it was possible to find capillaries which appeared to have ruptured into them.

The hemorrhagic cyst represented a multilocular endothelial space full of red blood cells. Several smaller ones were found.

Cortical Bone: The cortical bone appeared as a series of parallel layers of vertical spicules, widely separated by an overgrowth of connective tissue in the haversian canals. The capillaries were greatly distended and were surrounded by numerous dilated lymph spaces presenting a picture of lymphatic obstruction with
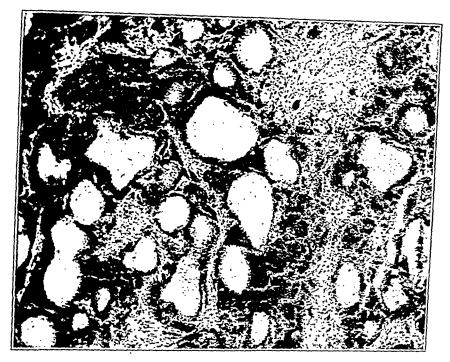
Fig. 6.—Photomicrograph of an area in the medullary cavity. The tumor is composed of many spaces full of lymph and surrounded by several rows of small, round cells. Hematoxylin-eosin stain; × 100.
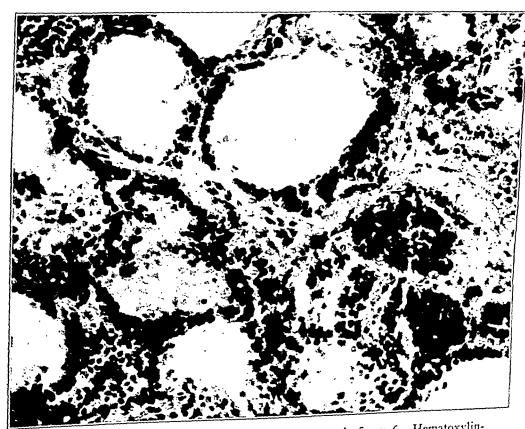
Fig. 7.—A higher magnification of the section shown in figure 6. Hematoxylin-eosin stain; × 500.

dilatation rather than one of autonomous new growth of lymph channels. The perivascular relationship of lymph spaces to capillaries and venules was constantly maintained.

Old osteophytes were seen to undergo resorption, but production of new bone was also conspicuous. The resorption did not appear to depend on osteoclastic activity, for osteoclasts were seldom observed.

Marrow Cavity: The medullary cavity was occupied by a diffuse overgrowth of fibrous connective tissue throughout which were scattered interlacing spicules of bone, dilated blood spaces and perivascular lymph channels. In general the structure was like that of the subperiosteal zone except that the growth was comprised chiefly of multicystic lymph spaces and showed less diffuse cellular overgrowth. No fatty or hematopoietic elements were present.

Summary of Microscopic Observations: The histologic picture was that of a tumor both angioblastic and osteogenic in its tendencies. The production of bone was not derived from the tumor-forming elements; rather the formation of new lymph spaces would appear to favor the theory of a nutritional stimulation to osteogenesis.

The angiomatous elements appear in their most natural state in the cortical bone as dilated perivascular lymphatics, whence they may be traced inward to the medullary cavity and outward to the zone of subperiosteal ossification; in either location the growth assumes a neoplastic character of tissue spaces lined by endothelial tumor cells, containing tumor cells and lymph in their lumens and surrounded by a diffuse growth of tumor cells. In the periosteum the growth is diffuse along tissue spaces and seems restricted to the periosteum overlying the proximal end of the shaft.

NOTE.—In December, 1932, approximately ten months after the amputation, metastases developed which involved both angles of the mandible, the occiput of the skull and the forehead in the midline at the root of the nose. The patient was readmitted to the hospital. There was no roentgenologic evidence of metastases to the lungs or to the other long bones.

The case was registered with the Bone Sarcoma Registry and was diagnosed as "Ewing's sarcoma."

The patient died on July 26, 1933, at the age of 6½ years. Autopsy was performed on July 27, 1933.

Autopsy.—The anatomic diagnosis was: Ewing's tumor (lymphangio-endothelioma), primary, in the left tibia with metastases to the skull, vertebrae, iliac bones, right femur, ribs, left lung, pericardium and diaphragm.

The body was that of a small boy, 6½ years of age, 3 feet and 2 inches (96.44 cm.) in length; the estimated weight was about 35 pounds (15.9 Kg.). The skin was light brown, that of a negroid type of Puerto Rico. The features, likewise, had a negroid appearance. The left lower extremity had been amputated at the midthigh, leaving a small stump, 3 inches (7.6 cm.) in length, completely closed by skin and soft tissue. The head had a grotesque appearance. It possessed, more or less, the shape of a parallelogram, the longer diagonal, from the vertex to the chin, measuring 12 inches (30.48 cm.), and the shorter diagonal, from the occiput to the forehead, measuring 9 inches (22.86 cm.). This peculiar shape resulted, in part, from a large tumor covering the occipital regions of the skull, measuring 7 by 3 by 2 inches (17.78 by 7.6 by 5 cm.). A smaller metastasis, 1½ inches (3.77 cm.) in diameter, overlay the right parietal area. Both growths were firm but not hard. The forehead was covered by a metastatic tumor, which extended in a horizontal direction from the middle of the right supra-orbital base

to the outermost border of the left supra-orbital base. It was 4 inches (10.16 cm.) long and raised about 1 inch (2.5 cm.).

Both eyes were almost completely everted from their sockets. The angle of the right mandible was enlarged by a spherical mass, 1½ inches (3.77 cm.) in diameter, firm and bony. The entire left ramus of the mandible was involved in a huge globular swelling, which extended to include the left submaxillary area and the left maxilla. This mass was, roughly, about 5 inches (13 cm.) in diameter. The skin overlying it was green and discolored.

There was a small opening, about 2 inches (5 cm.) in front of the lobule of the left ear, from which exuded some foul-smelling pus. The oral cavity was almost completely filled with a bulging tumor, covered by mucosa, which was undoubtedly continuous with the growth in the left mandible and maxilla. The teeth were distorted and irregular; many were loose and could be withdrawn from their sockets. No lymph nodes were palpable in the cervical, supraclavicular, axillary or inguinal regions.

The chest, externally, showed some small metastases to the ribs, one involving the right sixth and seventh ribs in the anterior axillary line, another involving the left ninth rib.

In the upper third of the right femur there was palpable a nodular, firm swelling, undoubtedly a metastasis.

The body was extremely wasted. On section, there was no subcutaneous fat. The muscles appeared wasted. When the abdominal cavity was opened, the peritoneum was smooth and shiny. The liver seemed slightly enlarged and low, extending about 1 inch (2 cm.) below the costal margin.

An exploration of the abdomen revealed a retroperitoneal tumor overlying the body of the second lumbar vertebra in, and to the left, of the midline, and a second mass filling the left iliac fossa. The diaphragm was at the fifth rib on the right and at the fifth space on the left, in the anterior axillary line. The right dome was inverted by a globular mass, undoubtedly occupying the thoracic cavity.

Chest: When the soft tissue of the chest was reflected, the metastases to the ribs on the right and left were seen to lie precisely at the respective costochondral junctions. The metastasis on the right was approximately spherical, 2½ inches in diameter; it extended into the right pleural cavity and was attached to the lower lobe of the right lung. This was the mass which depressed the diaphragm.

Heart: The heart weighed 100 Gm. Epicardial fat was absent. A small mass, ¼ inch (0.6 cm.) in diameter was attached to the outer surface of the parietal pericardium, posteriorly. The pericardial cavity contained about 25 cc. of clear fluid. The heart was otherwise normal.

Lungs: The right pleural cavity contained 25 cc. of fluid. The left contained about 50 cc. The lungs weighed 360 Gm. They were markedly edematous. The left lung contained a metastasis in the lower lobe, ½ inch (0.77 cm.) in diameter, directly beneath the pleura. This was soft on section and bulged from the cut surface.

Liver: On the superior posterior aspect of the right lobe, there was a minute metastasis, ¼ inch (0.6 cm.) in diameter. The liver otherwise was normal.

The spleen, kidneys, suprarenals, pancreas, gastro-intestinal tract, bladder and testes were essentially normal.

Bones: The vertebral column showed a slight curvature with the convexity to the right. On section through the vertebrae, the marrow was bright red.

Metastases which had a contrasting yellow color were found occupying the bodies of the lower sixth dorsal and the second, third and fourth lumbar vertebrae. These were usually distinctly central in position and did not involve the intervertebral disks. The metastasis in the second lumbar vertebra was continuous with a mass 2 inches (5 cm.) in diameter, already described, which overlay the anterior aspect of the body retroperitoneally.

Iliac Bones: The left iliac bone contained a tumor that completely filled the fossa, measuring 4 by 3 inches (10.16 by 7.6 cm.). This mass invaded the bone and cartilage of the iliac crest. It was relatively soft and could be excised with a knife. It was yellow and somewhat gritty on section. The left ilium contained a smaller metastasis in the fossa, roughly 1 inch (2.5 cm.) in diameter.

Femur: An incision was made over the medial aspect of the right femur disclosing a metastasis, about 1 inch (2 cm.) in diameter, occupying the cortex and medulla of the bone, at the level of the upper third.

Head: When the scalp was reflected virtually both the parietal bone and the occipital bone were replaced by grayish-white, soft tumor tissue. The occipital mass already measured and described was the largest, but the tumor replaced virtually the entire parietal and occipital areas from left to right. These metastases could be excised from the skull. They were grayish white, soft and extremely moist on section, but contained yellowish, fatty areas, presumably degenerated, and were streaked with gritty deposits of bone. The occipital bone was considerably thickened and measured ½ inch (1.77 cm.) in thickness. The temporal bones were 1/16 inch (0.15 cm.) and the frontal bone was ⅛ inch (0.3 cm.) in thickness. The inner surface of the skull was unevenly eroded and ulcerated and also showed flat elevations of tumor growth. The outer surface of the dura was extensively covered with metastases. The inner surface was smooth and not involved. Tumor tissue replaced the crista galli in the midline and extended into both orbital fossae. In these sites, the tumor was almost gelatinous.

The brain weighed 1,050 Gm. and was pale and soft, but otherwise was not unusual.

Microscopic Examination: Examination of the various metastases showed tumor tissue composed of small, round cells, approximately the size of lymphocytes. Each cell possessed an oval nucleus which was richly chromatic, a solitary nucleolus and a scattering network of chromatin. The cytoplasm was rarely visible. There was marked uniformity in the size and shape of the tumor cells. There were large numbers of mitotic figures.

In the metastases, the growth was diffuse and exhibited none of the angioblastic tendencies of the primary tumor. There was a delicate supporting reticulum. Many areas showed widespread necrosis.

No metastases were found in the deep iliac lymph nodes. The cells were identical in appearance with those in the primary growth.

COMMENT

So many cases of Ewing's tumor are on record that the mere addition of another case would serve little purpose. I feel, however, that the case reported is unique in that the histologic picture was such as to permit tracing the tumor to its site of origin. I feel, too, that there is a great deal of contradiction between the old and the more recent discussions of this subject, and that an exposition of these differences may serve to clarify the understanding of the disease.

There can be little doubt that the growth is an example of Ewing's tumor. The age of the patient, the clinical history and the characteristic error in diagnosis (osteomyelitis), the gross characteristics, particularly the limitation to the shaft without involvement of the epiphysis, and the invasion of the haversian systems and of the marrow cavity, with reactive formation of bone and fibrosis, all seem typical. The old idea of an osteolytic tumor located in the midshaft of a long bone should undoubtedly be abandoned.

I am aware of the dangers of attempting to trace the origin of a tumor on histologic grounds alone. In no field is the opportunity for error so great as in that of endothelial tumors, the characteristics of which, lying intermediary between those of epithelial and those of mesoblastic tumors, render confusion in either direction most likely. Yet there can be no doubt that the tumor originates spontaneously from the endothelium of lymph vessels since a direct continuity is established between seemingly normal though dilated lymph spaces in the haversian canals and the abnormal ones in the subperiosteal and medullary zones. Moreover, proliferating endothelium, multiple layers of endothelium and sprouts of endothelium growing out into connective tissue were frequently observed. Further, the tumor maintains its angioblastic arrangement throughout and produces a secretion of lymph fluid.

Although the structure of Ewing's tumor is described in most cases as diffuse, exceptions to this are frequent. Endothelial tumors are classified by Ewing [6] as: (1) interfascicular (consisting of thin layers of cells growing between strands of connective tissue); (2) alveolar (composed of large groups of cells resembling adenoma); (3) plexiform (composed of convoluted columns showing papillary projections), and (4) diffuse (having the usual appearance of Ewing's tumor). The first three histologic types were present in the tumor in the case reported.

In discussing the theories of the origin of endothelial tumors, Ewing [6] mentioned several possible factors: (1) lymph stasis with lymphangiectasis; (2) a neoplastic growth of lymph vessels, and (3) a heteroplastic growth of lymph vessels into granulation tissue. He quoted Ribbert, who believed that lymph stasis with resultant pressure would inhibit, rather than favor, a process of growth. Certainly lymph stasis is present but whether it is a cause or a result it is impossible to say. Because of the age of the patients and other factors I prefer to subscribe to Ewing's view that the origin of lymphangioma must be attributed to a predisposition of tissue resulting from an embryogenic disturbance.

6. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, pp. 252 and 334.

WHERE DOES EWING'S TUMOR ARISE?

Endothelial tumors in general are usually believed to arise from the endothelium of small blood vessels and lymph spaces. The process represents either a conversion of normal endothelium along the channels of origin into endothelial tumor cells or a diffuse overgrowth of endothelial tumor cells or both. An origin from the highly specialized endothelium lining large vessels is of course improbable on oncologic principles and has no basis of fact in the experience of pathologists. An origin from perivascular lymph spaces in the haversian canals and beneath the periosteum is thus in harmony with the origin of endothelial tumors elsewhere.

LYMPHATICS OF BONE

The information to be derived from the literature regarding the nature and distribution of lymphatic channels in bone is fragmentary and confusing. Many standard textbooks of histology and anatomy make little or no mention of this subject.

Piney,[7] Kolodny[8] and more recently Campbell[9] have undertaken to demonstrate experimentally the course of osseous lymphatics, with conclusions that are not always in harmony.

The chief point of controversy among most workers concerns the presence or absence of lymphatic channels in the bone marrow, and from the standpoint of the present paper the question is of paramount importance, because it would establish for all time the origin of Ewing's tumor.

The existence of periosteal and intracortical lymphatics is a matter of unanimity of opinion. Langer,[10] who described periosteal lymphatics in 1875, is said by Campbell[9] to have been the first to do so. Shortly thereafter Budge[11] and later Schwalbe[12] pictured a network of periosteal lymphatics communicating with intracortical lymphatics, into which Schwalbe succeeded in injecting dyes. More recently Rauber,[13] quoted by both Kolodny[8] and Campbell,[9] described the presence of

7. Piney, A.: Carcinoma of the Bone Marrow, Brit. J. Surg. **10**:235, 1922.

8. Kolodny, A.: The Relation of the Bone Marrow to the Lymphatic System, Arch. Surg. **11**:690 (Nov.) 1925.

9. Campbell, E.: Periosteal Lymphatics, Arch. Surg. **18**:2099 (May) 1929.

10. Langer, Carl: Ueber das Gefässystem der Röhrenknochen, Vienna, K. Gerold's Sohn, 1875.

11. Budge, A.: Die Lymphwuerzeln der Knochen, Arch. f. micr. Anat. **13**:87, 1876.

12. Schwalbe, G.: Ztschr. f. Anat. **2**:131, 1877.

13. Rauber, A.: Lehrbuch der Anatomie des Menschen, ed. 9, Leipzig, Georg Thieme, 1911, pp. 5 and 17.

endothelium lining the haversian canals. Kolodny quoted Rauber, as follows:

This endothelium forms the external wall of the perivascular lymph channels surrounding the single or multiple blood capillaries coursing in the central portion of the haversian canals. These perivascular lymphatics anastomose widely with the abundant lymphatics of the periosteum. Prussian blue injected into the periosteal lymphatics freely penetrates the substantia compacta and stops abruptly at the endosteum.

Piney [7] made injections into lymphatic channels in the periosteum. The injected materials passed into the cortical bone and thence into the endosteum, but he was unable to demonstrate any connection between the periosteo-endosteal lymphatics and the marrow. When injection was made directly into the marrow cavity, the material passed by way of definite medullary channels to the veins at the large foramina where it emerged. Piney concluded that there were no lymph channels in the marrow cavity.

Kolodny [8] agreed as to the presence of periosteal and intracortical lymphatics and himself discovered a large lymph channel in the femur of the dog which pierced the compact bone obliquely in the proximal portion of the shaft, just below the intertrochanteric line. He next conducted a series of admirable experiments designed to establish the existence of medullary lymphatics. Kolodny stated that his approach to the problem was physiologic rather than anatomic, and admitted the improbability of antomic demonstration of lymphatic channels in the bone marrow.

He injected dyes, such as india ink and carmine, into the marrow cavity in animals and recovered the material from the regional lymph nodes. The deep iliac nodes were the regional lymph nodes for the lower extremity, while the cervical nodes were said to drain the upper extremity.

A powerful clinical argument against the existence of marrow lymphatics, namely, the absence of regional lymphadenitis, was refuted by Kolodny,[8] who held that the regional lymph nodes do react, but that the proper ones are rarely examined, namely, the deep iliac and the cervical. Kolodny concluded that the bone marrow is "directly related to" the lymphatic system without offering the anatomic presence of lymph channels in the bone marrow. Piney [14] later criticized Kolodny's conclusions, saying, in brief, that the dyes could readily enter lymph nodes via the blood stream, and that this was probably the channel in Kolodny's experiments.

More recently, Campbell [9] succeeded in making injections into a plexus of periosteal lymphatics in infants and in animals. He was unable

14. Piney, A.: The Relation of the Bone Marrow to the Lymphatic System, Arch. Surg. **13**:615 (Oct.) 1926.

to demonstrate communication with intracortcial lymphatics. His method consisted in inserting the point of a fine glass cannula directly into the periosteum and injecting dilute india ink under low pressure.

Cowdrey [15] described lymphatic vessels and perivascular lymph spaces in the haversian canals.

One may conclude by saying that a great deal of histologic and experimental evidence has been accumulated; that as to the presence of periosteal and intracortical lymphatics in the haversian canals there is thorough agreement; that the existence of lymphatics in the bone marrow has never been demonstrated, and that the inconclusive evidence of Kolodny [8] has been seriously questioned.

Obviously, if there are no lymphatics in the marrow cavity, tumors of lymphatic endothelium cannot originate there. This is in keeping with the more recent anatomic studies of Geschickter and Copeland,[3] which appear to indicate that the origin of Ewing's tumors is either subperiosteal or in the cortex, *precisely the sites where lymphatic endothelium is known definitely to exist.*

Connor [5] attributed the origin of Ewing's tumor to a reticulo-endothelial cell in the bone marrow, but this conception is rather vague. Ewing has always suspected that the origin might be from perivascular lymphatic endothelium, as have more recently Geschickter and Copeland. However, in most of the material studied, the histologic picture was that of a diffuse endothelioma in which, from the nature of the structure, it was impossible to trace growth directly to lining endothelium.

I feel that the tumor in the case reported is derived from the perivascular lymphatic endothelium lying in the haversian spaces and in the subperiosteum, and that this probably represents the site of origin of Ewing's tumor in all cases. Certainly such a hypothesis would explain the early destruction of the haversian system, which is pathognomonic.

A medullary origin would seem less likely, for the reason that no one has ever demonstrated the presence of lymphatic endothelium in the bone marrow, and because the bulk of the clinical and histologic evidence is contrary to the existence of lymphatics in the bone marrow. If, as Connor suggested, the tumor arises in a primitive reticulo-endothelial cell in the bone marrow, how does one explain the absence of epiphyseal involvement in the marrow, in which reticulo-endothelial cells are surely just as numerous?

SUMMARY

1. A case is reported of a primary intracortical and subperiosteal lymphangio-endothelioma, so designated because the tumor could be traced to the perivascular lymphatics of the haversian canals and to

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15. Cowdrey, E. V.: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, p. 722.

those beneath the periosteum, and because the tumor cells secreted lymph.

2. The clinical course and the gross and microscopic pathologic picture of this tumor satisfied every criterion of so-called Ewing's tumor.

3. No field of pathology has been more confusing than that of endothelial tumors of the bones. This was true in the past, and is true at present, for many cases reported as instances of Ewing's tumor represent other types of growth.

4. The conception that Ewing's tumor is a primary osteolytic tumor of the medullary cavity is erroneous and should be displaced.

5. Probably in every true case, Ewing's tumor is a lymphangioendothelioma, originating in the lymphatic endothelium of the haversian canals and in that beneath the periosteum. Involvement of the medullary cavity, while prominent, is probably secondary.

6. This concept is in harmony with anatomic knowledge of the lymphatics of the bones, for lymphatics have never been demonstrated in the bone marrow, whereas perivascular lymphatics in the cortex and beneath the periosteum are well known. Even should the existence of lymphatic spaces in the bone marrow be demonstrated at a future date, the validity of the concept would not be destroyed, since medullary involvement might readily occur by transformation of normal lymph endothelium into a neoplasm.

OSTEOMYELITIS OF THE ILIUM

CARL E. BADGLEY, M.D.

Surgeon in Charge, Division of Orthopedic Surgery, Henry Ford Hospital

DETROIT

INTRODUCTION

My interest in osteomyelitis of the ilium was first aroused in 1924 when several cases with extensive chronic lesions accompanied by marked deformities of the hips came to my attention. The apparent hopelessness of these cases led me to a review of the literature on osteomyelitis of the ilium. There were surprisingly few articles on the subject in English, and these were chiefly case reports of acute osteomyelitis of the ilium and dealt with the acute phases of the disease. Two outstanding articles were found in the foreign literature, Gouillioud's and von Bergmann's, both of which advocated what seemed at the time radical measures, but which later, in the light of experience, I have accepted as sound.

My interest has been maintained in this subject for the past six years by new cases, generally of chronic osteomyelitis of the ilium, coming under observation. I am reporting 24 cases, 21 of which have been under observation for the past six years.

It is interesting to note that there is no article published, which I have been able to find after a very diligent search, dealing with *chronic* osteomyelitis of the ilium, with the possible exception of von Bergmann's, which deals in the main with acute osteomyelitis of the ilium, but also presents reports of chronic cases. There is no doubt that cases of osteomyelitis of the ilium, acute and chronic, are seen in other clinics, but with such relative infrequency that, unless some one was particularly interested in the disease, the idea of radical surgical intervention might well not be considered. From conversation with various surgeons, the impression is gained that palliative treatment, such as incision and drainage of local abscesses, possibly associated with local curettements and local resections, is the usual treatment employed.

Acute osteomyelitis of the ilium is generally regarded as a rare lesion attended with a grave prognosis. Those persons fortunate enough to survive the acute infection frequently present severe disabilities such as a chronic osteomyelitis with prolonged suppuration which may eventually lead to amyloidosis, septicemia and death. A high percentage of the survivors of the acute infection present severe lesions of the hip joint including bony ankylosis, fibrous ankylosis, or, as in three of my cases, pathologic dislocation of the hip.

The treatment advocated for acute osteomyelitis of the ilium in the recent literature seems much too conservative for cure of the lesion. In general, the trephine operation is advocated with local resections for local lesions. Resection of the ilium is generally mentioned as a possibility, but no single case was reported in which a resection was performed other than a partial resection done by Simmons.

It is of interest to note the absence of any detailed report of the further progress of the lesion in cases of acute osteomyelitis of the ilium. Several authors, Simmons and Bearse particularly, each mention a case. It would be interesting to ascertain the end-result in these acute cases in which the treatment is merely trephination of the ilium to drain an abscess in the internal iliac fossa.

Of my 24 cases, 20 were cases of chronic osteomyelitis of the ilium in which inadequate treatment by palliative and ultra-conservative measures was employed. There is a real need to present a

Incidence of Acute Osteomyelitis of the Ilium Contrasted with Acute Osteomyelitis

	Of All Bones	Of Ilium
Lannelongue	24	1
Lucke	24	1
Volkmann	29	0
Schede	24	2
Kocher	30	1
Hanga	414	4
Heidenhain	46	1
Mllehner	55	3

review of the excellent work which has been done on osteomyelitis of the ilium. For there are certain known facts in regard to osteomyelitis of the ilium which place the treatment of infection of this bone on a definite basis, which, if properly followed, will give excellent results, tending to lower greatly the mortality rate, prevent invasion of the hip and sacro-iliac joints and eliminate to a considerable extent the cases of chronic osteomyelitis of the ilium. In my cases the poor results were in the failure of application of these facts, and not in the facts themselves.

INCIDENCE

Although osteomyelitis of the ilium is considered an infrequent bone infection, 20 patients were treated at the University Hospital at Ann Arbor, Mich., and another patient whose case I am reporting was treated elsewhere, between 1924 and 1929. At the Henry Ford Hospital, Detroit, 3 patients have been treated in the past two years.

Various observers have reported the incidence of osteomyelitis of the ilium in their experience (table).

Klemm reported 1,469 cases of osteomyelitis, 23, or 1.66 per cent, involving the pelvis, and 20 occurring in the ilium.

Trendel, in fifty years' experience, reported 1,058 cases of osteomyelitis with 1,279 bones involved, of which 169 were flat or short bones. Twenty-eight were in the pelvis, 25 involving the ilium. This gives approximately 2 per cent incidence of osteomyelitis of the ilium.

Frohner, in forty years' experience, reported only 4 cases involving the ilium in his series. He combined the reports of various authors, namely, Lucke, Volkmann, Schede, Kocher, Lannelongue, Haaga and Brun. From these reports he estimated that 3.3 per cent of all cases of osteomyelitis involved the flat or short bones, with 33 per cent of these involving the ilium, or about 1 per cent. Von Bergmann reported seventy-one cases of osteomyelitis of the pelvis, about sixty of which involved the ilium. His intense interest in this lesion undoubtedly was a factor in his large series of cases, the largest group ever recorded.

Monsaingeon stated that in an active service at the Clinique Chirurgicale Infantile, only 14 cases of acute osteomyelitis of the ilium were seen in thirteen years. Peeremans stated that in a hospital for children only 7 cases of osteomyelitis of the ilium, or 1.2 per cent, were seen in a total of 548 cases, but Michelson reported 137 cases in a total of 1,008, or 14 per cent, in a hospital for adults. He concluded that osteomyelitis of the ilium occurs less frequently in the prepuberty than in the postpuberty period.

<center>AGE</center>

The greatest incidence of osteomyelitis of the ilium is before the period of complete fusion of the epiphyses, generally before 25 years of age. Von Bergmann emphasized that osteomyelitis of the ilium also developed in older persons. In a series of 71 cases the age incidence was as follows: persons under 15 years, 12; those from adolescence to 21 years, 27; older persons, aged from 25 to 40, 21, and those older than 40, 11.

In my series 5 were over 25 years of age. However, one of the 5 had the onset of her illness at 10 years of age.

Monsaingeon stated that Cance reported the case of the youngest patient on record, that of an infant 16 days old. Broca reported a case of an infant 2 months old, and Fleury that of an infant 6 weeks old.

The usual age period is under 25, but the condition may occur at any age. My youngest patient was 20 months old and the oldest 75.

<center>LITERATURE</center>

The first comprehensive article on osteomyelitis of the pelvis was published in 1883 by Paul Goullioud. Entering his surgical career coincident with the development of aseptic surgery, and associated with Ollier at a period when Ollier was tremendously interested in bone infection, subperiosteal resections and bone regeneration, Goullioud was in a perfect environment for the development of his thesis. That

he took advantage of his opportunity may be attested by any one who reads his paper, for it presents the problem of osteomyelitis of the pelvis in such a complete and accurate fashion that it might well serve today as an authoritative document on this subject.

From a surprisingly accurate knowledge of the development of the bones of the pelvis, associated with Ollier's teachings of the importance of the juxta-epiphyseal zone in long bones in the development of osteomyelitis, Goullioud concluded that the bones of the pelvis may be regarded as analogous to the long bones in their skeletal development and in their susceptibility to infection. "The pelvic bones grow by cartilaginous margins as do the long bones at their ends, and the limiting parts of these cartilages correspond to the epiphyseal cartilages of the long bones." With this developmental analogy of the bones of the pelvis to the long bones, Goullioud conceived that the mechanism of infection would occur in the juxta-epiphyseal zones of the pelvic bones as it does in the long bones. With this idea as a basis, Goullioud divided osteomyelitis of the pelvis into two groups with distinct clinical syndromes corresponding to two periods of development of the bones of the pelvis. The first period extended from infancy to puberty, at the end of which period the three bones composing the acetabulum fuse. The second period commenced with the ossification of the acetabulum and the appearances of the marginal epiphyses, and extended to the time of fusion of the marginal epiphyses, at about 25 years of age.

The first period was characterized by a diffuse infection almost invariably occurring at the border of the acetabulum. This location is the site of the numerous ossification centers presenting spongy juxta-epiphyseal tissue which corresponds to Ollier's juxta-epiphyseal zone in the long bones which he felt was the most susceptible to infection. He states the infection might be periacetabular, in which case it spreads through the ilium, or it might be intra-acetabular and involve the hip joint proper. The second period was characterized by lesions occurring about the marginal epiphyses. The chief points of involvement of this late osteomyelitis of the ilium are the posterior and anterior superior spines of the ilium, the crest of the ilium and the inferior anterior spine.

Goullioud believed this classification was of great importance in the consideration of the treatment of osteomyelitis of the ilium. He felt that operative intervention for osteomyelitis of the pelvis should be more courageous. In the acute form, where the infection involved the supracotyloid area or the marginal juxta-epiphyseal area, he advocated an extensive drainage and removal of diseased bone. Where the hip joint itself was involved, he advised a resection of the ilium. In the subacute and chronic form the intervention varied with the lesion. according to its age and anatomic location.

There are many interesting historical facts presented in Goullioud's paper. He refers to Boucher, who in 1779 was the first to trephine the ilium to drain an internal iliac abscess resulting from an osteomyelitis of the pelvis. He stated that Leaute did the first recorded resection of the crest of the ilium. He reported a subperiosteal resection of the ilium performed by Larghi de Verceil in 1845, with recovery. He gives credit to Ollier for popularizing resection of bone as a proper procedure in the treatment of extensive osteomyelitis of the ilium as well as other bones, and for the important recognition that regeneration of the bone would occur if a subperiosteal resection were performed. He has collected a large number of recorded cases of osteomyelitis of the pelvis from the literature as well as reported his own cases. His bibliography is extensive.

Von Bergmann of Riga, in 1906, reported 71 cases of osteomyelitis of the pelvis in which he had treated the patients. He was greatly impressed by the scarcity in the literature of reported cases of this lesion, and by the high mortality rate. He felt that the high mortality rate occurred because the diseased area was not sufficiently excised.

He recognized that temporary cures would occur in low grade infections, either spontaneously or after palliative operations, but that after a longer or shorter period the patient would get sick again. He emphasized particularly the need of removing the diseased bone, for if not removed, it acts like a cistern for the formation of new abscesses. He therefore urged radical methods in the treatment of this lesion, with resection of all of the diseased bone.

Von Bergmann stated that Miller's hemorrhagic osteomyelitis, Brun's and Hancell's rarefying type of osteomyelitis and the diffusely infiltrating spongiosa type of osteomyelitis occur in osteomyelitis of the ilium as well as of the long bones.

He recognized the rare formation of sequestrums and the frequent perforation of the tables of the ilium. He also noted the marked thickening and sclerosis in the chronic cases of osteomyelitis of this bone.

Von Bergmann advocated the most radical measures for osteomyelitis of the ilium. He said: "The later in the disease we are called to operate, the more wide should be the resection; if earlier, we can get away with partial resection, but in youth the best treatment is resection down to the epiphyseal cartilage."

He divided the types of treatment used in his 71 cases into three main groups:

Group I: Partial resection
    A. Disease of marginal epiphysis or other localized disease
        Ilium   13 cases
        Ischium   2 cases
        Pubis   2 cases
        None of these patients died.

B. Partial resection in the diffuse type
    Ilium   20 cases
    Pubis   1 case
    Three additional cases of tuberculosis in which the patients were
        moribund.
    In this subdivision, 17 patients died.
Group II: Total resection
    There were 28 cases in this group. The hip joint was resected
        with the ilium in 15, and there were 7 fatalities.
Group III: Extirpation of the os innominatum and disarticulation of
    the lower extremity
    There were 3 cases in this group, and of these 1 was fatal.

Von Bergmann felt that the mortality rate in subdivision B of group
I would have been much lower had he done a total, rather than a partial,
resection. He concluded that only a complete resection of the diseased
pelvis could better the poor prognosis.

It is quite possible that the apparently radical nature of von Berg-
mann's operative treatment delayed the acceptance of the truth of his
statements. A review of the cases reported in the literature since
von Bergmann's report shows surprisingly few patients treated as he
advised.

Monsaingeon, in 1911, reported 14 cases of acute osteomyelitis
of the ilium in thirteen years' experience. He believed Goullioud's
division of the disease into two age periods was what he termed very
exclusive. He stated there were two main types: a subperiosteal type
of lesion and a lesion involving the growing bone area, a true osteo-
myelitis. He subdivided the cases into three clinical groups: "(a) sub-
acute type where the lesion is circumscribed in the beginning without
severe symptoms either local or general; (b) acute type where the
primary lesion is very serious, rapidly diffuse, and often accompanied
by invasion of the hip; (c) very acute type where the general infection
dominates the picture and where the local lesion is not in proportion to
the severity of the infection, very probably a true septicemia type."
With his theory of a subperiosteal lesion associated with an osteoperi-
ostitis as a clinical lesion, he advocated incision and drainage in the
cases of superficial subperiosteal abscesses without marked bone lesions.
He advises trephining the ilium if there is an abscess of the internal
iliac fossa to drain properly this abscess, or if the ilium is markedly
infected. He stated that von Bergmann's results in resection were not
as successful as he maintained and advocated resection only as a last
resort if trephining failed to clear up the symptoms. He mentioned
several rare complications of osteomyelitis of the ilium reported by
various authors, citing a case of peritonitis of the pelvis following a
prevesical phlegmon arising from an osteomyelitis of the ilium; a case
of spontaneous rupture of an abscess from osteomyelitis of the ilium

into the rectum; a perforation of the colon in a case of sacro-iliac invasion from osteomyelitis of the ilium; several cases of severe arterial hemorrhage, and, phlebitis of the iliac vein, as well as pyarthrosis of the hip or sacro-iliac joint.

In 1915, Simmons, discussing "The Treatment of Osteomyelitis," reported 2 cases of osteomyelitis of the ilium out of 97 cases and stated that when a flat bone as the ilium is affected drainage is about all that can be done. "Many cases seen early will heal without further trouble, but if necrosis does occur, subperiosteal resection should be done in six to eight weeks." In the first case three incisions were made and abscesses drained, and later two other operations for sequestrums were reported. In the second case, a trephine operation was followed later by resection of a greater part of the ilium. Both patients had sinuses at the time his paper was written.

In 1917, Speese and Skillern reported a case of acute osteomyelitis of the ilium in which they drained an abscess in the external iliac fossa and a month later drained an abscess in the internal iliac fossa by the trephine operation, apparent recovery resulting. Geist, in 1921, remarked on the paucity of the literature on osteomyelitis of the pelvis. He reported 6 cases, 3 of which involved the ilium. He emphasized two important points: (1) that in his 3 cases the pus always collected in the internal iliac fossa, and (2) that sequestration plays little part in osteomyelitis of the ilium. Geist advocated the trephine operation. His 3 patients were reported as cured. He stated that it was necessary in all of his cases to trephine in several places through the ilium before the pus could be reached.

Peeremans, in 1923, reported 4 cases of osteomyelitis of the ilium, in which incision, drainage and removal of the outer table were done. Trephine of the iliac fossa was performed in a case. He advocated resections only in the very severe cases and felt that trephining is the operation of choice for drainage of the internal iliac fossa. It is significant that pyarthrosis of the hip joint with resultant ankylosis developed in 2 of his cases.

Bearse, in 1924, reported 2 cases of acute osteomyelitis of the ilium in which he had treated the patients. He concluded: "If the ilium is perforated, incision and drainage is sufficient; with no perforation or unsatisfactory bone drainage, trephine operation of the ilium should be done. If, however, the process is an extensive one, partial or total resection should be done." In one case he used incision and drainage, and the wound was still draining at the time of his report; in the second case there was a perforation which he enlarged.

Koulouch, in 1924, reported a case in which the abscess was located in the internal iliac fossa and was drained directly on the inner side of the anterior superior spine. One and one-half years later he exposed

the ilium on both sides subperiosteally, finding a sequestrum posterior to the anterior superior spine and another in front of the sacro-iliac joint. A third sequestrum was found on the external surface just posterior to the acetabulum. There were several fistulas through the bone. All diseased bone was removed, but resection was not done as it was considered too radical a procedure.

Buonsanti, in 1924, reported in his experience 4 cases of acute osteomyelitis of the ilium with a mortality of 3, or 75 per cent. He emphasized the high frequency of an abscess in the internal iliac fossa, suggesting as possible factors that the pelvic periosteum perforates more easily and the iliac muscles strip more easily and the inclined plane of the pelvis tends to drain toward this fossa. He stressed the lack of spread of the infection to the viscera by continuity and gave credit to the pelvic diaphragm for preventing drainage into the true pelvis. He advocated incision and drainage in the very severe cases as a preliminary measure, quoting Professor Gatti: "Opening the wound helps not only the local but the general condition of the patient, attenuating the germs in the focus and removing just that much of the general symptoms due to the enclosed focus." In the diffuse cases he recommended trephining as practiced by Condamin. He believed resection should be done in the extreme case in which the squamous portion is bathed in pus.

Flickinger, in 1927, reported a case of osteomyelitis of the ilium for two reasons: first, because of the infrequency of a report of this type of case, and secondly, because no results after hospitalization have been reported.

In 1928, one of Cabot's case records contained a discussion on the differential diagnosis in a case in which the diagnosis of osteomyelitis of the ilium was not made until a biopsy done for the possibility of tumor demonstrated the inflammatory nature of the lesion.

This concludes a complete survey of the literature on this subject. As most of the articles are in a foreign tongue, and the work of several authors is so outstanding, a more comprehensive review than usual is given.

<div align="center">DEVELOPMENT</div>

There is a single center of chondrification for each of the three bones composing the hip bone. These centers soon fuse to produce a continuous cartilaginous hip bone which gradually assumes a definite form. An excellent conception of the cartilaginous anlage of the hip bone may be obtained from figures 1 and 2. A center of ossification appears in the main body of each of the cartilages, appearing first in the ilium (fig. 1), secondly in the ischium and lastly in the pubis. All three ossifying centers are shown in figure 2. The rami of the

ischium and pubis are united by bone in the seventh to eighth year. In the acetabulum the three bones composing the hip bone are separated by a Y-shaped cartilage until after puberty. The os acetabuli appears in this cartilage between the ilium and the pubis between the ninth and twelfth years. Union of the os acetabuli to the pubis occurs about puberty and soon afterward the acetabular portions of the ilium, ischium and pubis fuse.
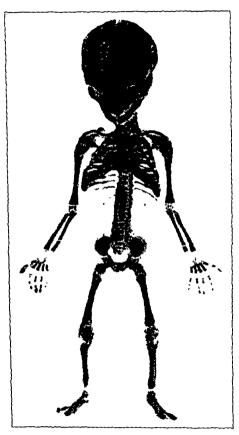
Fig. 1.—Five months old fetus showing ossification in the ilium but no ossification in the remainder of the pelvis. The cartilaginous continuity of the pelvis is well shown. (Published, by permission, from the article by Rudolph Skarda: J. Tech. Methods, to be published.)

Two secondary ossification centers for the ilium appear at about puberty, one for the crest of the ilium, and the other for the inferior spine of the ilium. The marginal epiphysis for the crest runs from the anterior superior spine of the ilium to the posterior superior spine. The appearance of the hip bone at puberty is well demonstrated in figure 3.

These secondary epiphyses fuse somewhere between the twentieth and the twenty-fifth year.

ANATOMY

It is impracticable to give a detailed anatomic description of the ilium, but there are several anatomic points which properly should be stressed. First, the structure of the ilium is irregular. The thicker parts of the bone consist of cancellous tissue enclosed within two layers of compact tissue which are lined by periosteum. The thinner parts, as at the bottom of the acetabulum and the center of the iliac fossa, are so thin that they are usually semitransparent and composed entirely of compact tissue.

Second, the internal and anterior sloping of the internal iliac fossa with its termination at the ileopectineal line is of great importance in explaining the great prevalence of abscess formation in the internal iliac fossa and the tendency to point anteriorly in Scarpa's triangle; blocked from passing further into the true pelvis by the structures attached to the ileopectineal line, gravity forces the purulent collection forward rather than backward.

ETIOLOGY

The organism which is chiefly responsible for osteomyelitis of the ilium is Staphylococcus pyogenes-aureus. The causative agent is rarely Stapyhlococcus albus, occasionally the pneumococcus, and infrequently the streptococcus. In the vast majority of reported cases and in practically all of my cases Staphylococcus aureus was the organism isolated. In one case tuberculosis was also recorded.

TRAUMA

Trauma undoubtedly plays some part in the development of osteomyelitis of the ilium. Bounsanti believes that the ilium is most frequently involved in an osteomyelitis of the pelvis because it is the most exposed to trauma. Definite trauma is frequently cited in the history, and was quite frequently reported in my cases.

PATHOLOGY

Goullioud was the first to recognize that the ilium did not differ essentially from the long bones in the anatomic structure. If one considers the epiphyseal structures of the ilium, the bone is quite analogous to a long bone with its shaft and epiphysis. Juxta-epiphyseal zones with areas of rapid ossification centers exist in the ilium as in the long bones. Infections localize in these areas exactly as Ollier has demonstrated their presence in the juxta-epiphyseal regions in the long bones. Later, Lexer's work with the injection of the nutrient vessels demonstrated the rich vascular plexus about the juxta-epiphyseal regions in the ilium, corresponding to the similar areas in the long bone (fig. 4). According to Lexer, the chief nutrient vessel enters the ilium on its

visceral side at the posterior portion of the arcuate line, passes forward and upward, and then bends sharply from above toward the acetabulum. It soon divides into numerous larger branches which quickly spread in all directions as fine branches. These branches reach upward toward the edge of the iliac fossa and downward toward the acetabulum. The acetabular part of the ilium receives the lowest tuftlike disseminated branches.
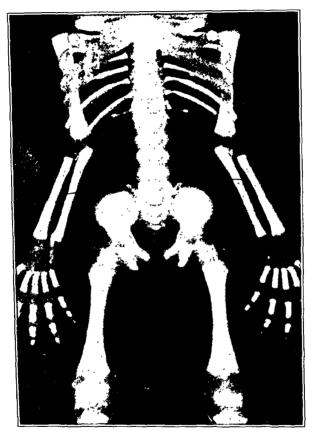
Fig. 2.—Five and one-half months old fetus showing calcification quite advanced in the ilium. Calcification is now present in the ischium and the pubis. (Published, by permission, from the article by Rudolph Skarda: J. Techn. Methods, to be published.)

It has been fairly well accepted that acute hematogenous osteomyelitis develops primarily in the dilated tufts of the metaphyseal vessels if the infected emboli are small, producing local areas of osteomyelitis. If larger, the nutrient vessel itself may become plugged, producing extensive necrosis of the bone dependent on it for nourishment. This extensive necrosis of bone rarely occurs in the ilium because of the rich blood supply introduced by the periosteal vessels. The architecture of

the ilium with its thin external and internal plates of cortical bone lined with periosteum and the small amount of spongy bone between aids greatly in prevention of massive sequestration.

Wilensky, in discussing the mechanism of acute osteomyelitis, spoke of the flat bones as structures derived exclusively from periosteal formation and from two opposing periosteal surfaces. He stated:

Practically speaking, the blood supply of the bone is a double periosteal vascular network. The nutrient artery circulation is negligible. The form of osteomyelitis which develops is determined by the physical characteristics of the vascular network; periosteal and subperiosteal forms of inflammation are the *rule*. A dominant characteristic of osteomyelitis of a flat bone is that its development immediately destroys the osteoblasts that are present. This explains the absence of any new bone formation. The extreme of this occurs when a defect occurs in the entire thickness of the skull bone; the defect remains permanently.

Under ordinary circumstances the integrity of the bone is preserved by the physical part of the double periosteal origin of the bone; circulation and repair is maintained from the opposing surface to that in which the inflammation is seated; and, as in other bones, the amount of destruction is limited to a superficial sequestration.

I cannot agree with Wilensky's statements in regard to osteomyelitis of the ilium. The ilium is not formed from periosteum but develops in cartilage from an ossifying center. The periosteum undoubtedly plays a part in its development, but it is essentially a bone formed from cartilage. The nutrient artery is not negligible as Lexer's injections demonstrate. Entrance of infection through the nutrient artery, at least until puberty, is probably the rule, as the vast majority of cases occurring before puberty show a diffuse osteomyelitis developing about the acetabulum in the zone of greatest vascularity of the nutrient vessel in the analogous juxta-epiphyseal region of the long bones. Monsaingeon has noted clinically a type of osteomyelitis which he classified as a periostitis with subperiosteal abscess formation. Monsaingeon also quoted Kirmisson and de Rocher, who believe that the periosteum itself may be the primary focus. This agrees with Wilensky's views. The frequency with which extensive bone changes developed in Monsaingeon's cases of supposed primary periosteal lesion weakens his theory of origin. The frequent evidence in reported cases of osteomyelitis of the ilium of perforation of one or the other table of the ilium or of both tables indicates that these abscesses are often formed within the cortices of the ilium and become subperiosteal from perforation rather than from a primary periosteal lesion. It is well known that a primary periosteal infection of the long bones occurs infrequently in contrast to the well recognized metaphyseal origin of the osteomyelitis with a subperiosteal abscess formation developed by the draining outward of the pus. Why should the ilium differ so radically from the long bones? Von Bergmann in

this connection stated that should one make simply a diagnosis of infected periostitis in these cases and not make any further observations on the bone, the patient would not be helped by a simple incision. The softened bone which is left behind is always the cistern for formation of new abscesses. The softening spreads farther to involve the other two components of the os innominatum, and either the hip joint or the sacro-iliac joint becomes infected.

In my cases of chronic osteomyelitis of the ilium, I did not note the absence of new bone formation that Wilensky described. In many cases involucrum formation was most extensive with numerous large and
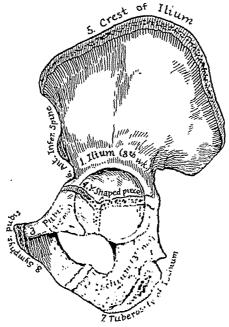
Fig. 3.—Ossification of the hip bone at about 13 years of age. (From Gray: Anatomy, Descriptive and Applied, Philadelphia, Lea & Febiger, 1924.)

small abscesses lined with dense eburnated bone. Sequestration of any great size was very rare, although in several cases numerous sequestrums were recovered. The lack of large sequestration can be easily explained by the thin cortical structure of the ilium, which by its structure could not make a sequestrum of any great thickness. The cortex is so thin that sequestrums formed could easily be digested by autolytic ferment, caries and phagocytosis.

I feel that the absence of extensive sequestration in the ilium is due not to the fact that the nutrient artery is never completely plugged, but to the generous blood supply of the double periosteum and its ability to nourish and develop bone. It is chiefly in this characteristic that osteomyelitis of the ilium differs from osteomyelitis of the long bones.

There are essentially two types of acute osteomyelitis of the ilium, one, a localized type, and the other, a diffuse type. Goullioud's observation that osteomyelitis of the ilium may be classified as the prepuberty and postpuberty types is in general sound. The diffuse type, arising in the periacetabular region and diffusing through the ilium and frequently into the hip joint or less frequently invading the sacro-iliac joint, occurs in the prepuberty type. The localized type occurs after puberty in the region of the marginal epiphyses, generally in the anterior portion of the ilium and less often in the posterior portion where sacro-iliac invasion sometimes occurs. Rarely is the crest itself involved, and primary periostitis is a rare occurrence.

With the exception of sequestration, the same pathologic process is present in osteomyelitis of the ilium that is noted in other bones. Two outstanding features should be observed: first, the frequent tendency to perforation, and second, the great tendency of an abscess to develop which points in the internal iliac fossa, stripping the visceral periosteum and the iliacus muscle from the internal table, and then tends to gravitate into Scarpa's triangle, posteriorly to the sacro-iliac joint or posteriorly at the triangle of Petit or at the greater sciatic notch. The absence of massive sequestration is also characteristic.

DIAGNOSIS

The diagnosis of acute osteomyelitis of the ilium is made difficult by several factors. First, the patients are acutely ill, and in many cases profoundly so; the general symptomatology frequently overshadows the local lesion, and the patient, dull and apathetic, does not offer much aid. Second, in the diffuse type of osteomyelitis of the ilium the lesion is situated so deeply from the surface that local palpation is not often of value. The local marginal involvement about the crest will frequently demonstrate tenderness on palpation, and the diagnosis of this type is much simpler. Third, the close proximity of the hip joint to the site of the infection associated so frequently with symptoms of involvement of the hip joint makes it difficult to differentiate between an acute osteomyelitis of the ilium and a pyarthrosis of the hip. Under guarded movements in osteomyelitis of the ilium, not involving the hip, a range of motion will be obtained which would be inconsistent with a pyarthrosis. Also, the deformity of a pyarthrosis of the hip is a flexion, abduction and external rotation, whereas in osteomyelitis of the ilium without pyarthrosis, the deformity tends chiefly toward flexion. Fourth, a frequent factor in the failure to recognize osteomyelitis of the ilium is undoubtedly its relative infrequency which makes one forgetful of its possibilities. This diagnosis should always be considered as a possibility

in a patient with high fever, leukocytosis, pain in the region of the hip, guarded motion of the hip and possibly local tenderness over the ilium.

Errors in diagnosis of this lesion are common.· In my series a large number of the patients were thought to have typhoid fever. Tuberculosis is frequently blamed, and rheumatism is often a diagnostic error. It is not unusual that patients with acute osteomyelitis of the right ilium are operated on for acute appendicitis. The most important differential diagnosis, however, lies in the distinction between osteomyelitis of the ilium, pyarthrosis of the hip and osteomyelitis of the upper third of the femur. Absence of tenderness along the shaft of the femur and
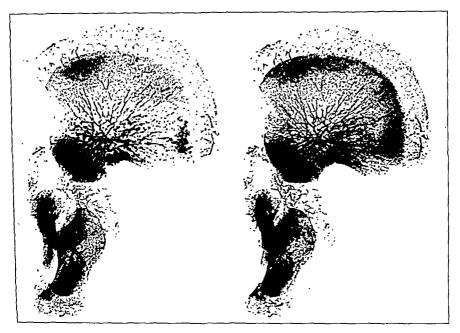
Fig. 4.—Nutrient vessel of the ilium. From Lexer's "Untersuchungen über Knochenarterien."

ability to move the hip, if motions are gently performed, point to osteomyelitis of the ilium.

In its clinical appearance acute osteomyelitis of the ilium may be divided into three types as described by Monsaingeon.

Type 1.—This type is localized osteomyelitis of the ilium, involving the areas about the crest or the spines of the ilium. The onset is of moderate gravity accompanied by a much less intense general reaction. The localization of the symptoms is quite definite, and because of the superficial location of the lesion, early abscess formation is noted. Diagnosis is much easier in this type of case, and treatment can be instituted much earlier. As the parts are easily accessible, the treatment

generally is adequate. These cases are most frequently seen in the postpuberty stage.

Type 2.—The diffuse type of osteomyelitis of the ilium, seen generally in the prepuberty period of life, is characterized by a much more severe local and general reaction with quite profound toxemia. Local symptoms are marked, but the general reaction is generally severe.

Type 3.—This type shows a most profound general reaction with the local symptoms insignificant in comparison. A septicemia with visceral metastases is generally present, and the osteomyelitis of the ilium is merely one of the local manifestations of severe and generalized infection.

SIGNS AND SYMPTOMS

The local symptomatology of osteomyelitis illustrates certain factors of importance in recognizing this lesion. Pain is the outstanding symptom and is generally felt in the hip, frequently in the region of Scarpa's triangle. Occasionally the pain is felt posteriorly, about the sacro-iliac joint and may be referred along the sciatic nerve (Kolouch's case). Geist emphasized the fact that in his three cases the pain was referred to Scarpa's triangle, and there was no pain in the internal iliac fossa with abscesses in this fossa. The deformity is an important sign in the differential diagnosis. With pyarthrosis of the hip joint there is generally a marked flexion, abduction and external rotation deformity. Any attempt at change of this position is resisted by the patient. In osteomyelitis of the ilium, with an abscess of the internal iliac fossa, there is a tendency to assume this same deformity. However, this deformity is much less marked and is chiefly flexion. Motion of the hip can be performed gently with the chief restriction in extension.

Tenderness to palpation is of definite value in the localized marginal lesions. Occasionally palpation reveals marked bony tenderness in the supracotyloid area. A diagnosis on such a finding was substantiated by roentgenograms and operation by Dr. V. L. Hart (verbal report) at Ann Arbor recently. Palpation should be made on either side of the ilium. In the chronic cases, one often feels a thick indurated swelling in the internal iliac fossa which is tender to palpation and which has not previously been noted by the patient. Rectal examination will frequently disclose swelling on the affected side of the pelvis which could not have been palpated in front.

The frequency of swelling in Scarpa's triangle should be noted in the subacute cases. Induration about the ilium associated with edema, prominence of the superficial veins and local heat can be made out occasionally.

The general findings of osteomyelitis elsewhere are seen here in that the temperature is high, chills are frequently recorded, there is a rapid pulse rate, and a high polymorphonuclear leukocytosis is generally present.

ROENTGEN EXAMINATION

In the acute case roentgen examination is of little value. With the improved soft tissue technic of today, one can occasionally visualize soft tissue swelling lateral to the outer cortex of the ilium, which aids somewhat. The roentgenograms taken later in the disease first show a mottled appearance with loss of sharp detail generally noted in the ilium. Later, the marked osteosclerosis, the so-called "marble appearance," is demonstrated. In my experience this generally means abscess formation lined by eburnated bone. Sequestration is rarely seen in roentgenograms. The changes noted in the roentgenograms in the chronic cases are frequently bizarre and make the diagnosis difficult from the roentgenologist's standpoint. A recent case record of Cabot in which a chronic osteomyelitis of the ilium was diagnosed as a sarcoma illustrates this difficulty. However, a good conception of the chronic case can often be obtained by roentgen examination, especially in the localized cases. Perforation is frequently noted on roentgen examination.

The localized abscesses just above the acetabulum in two of my cases are excellently demonstrated by roentgenogram (figs. 7 and 9).

In the chronic case the diffuse type of osteomyelitis of the ilium shows a dense thickened bone with areas of rarefaction here and there, and frequently bony overgrowth can be demonstrated on the external surface of the ilium (fig. 11).

TREATMENT

The treatment of osteomyelitis of the ilium may be divided into three phases of the disease: the acute, the subacute and the chronic stages.

The treatment of the acute phase is subdivided as to whether it is a diffuse or localized osteomyelitis. As Goullioud has shown, the age of the patient is of considerable aid in determining this point. The cases of the prepuberty type are generally diffuse, and the osteomyelitis begins in the pericotyloid region. The cases of the postpuberty type are generally localized, and the disease begins about the marginal epiphyses. Monsaingeon's subdivision of the acute group into the three types is as follows: (a) subacute or localized lesion, (b) acute or diffuse osteomyelitis and (c) very acute diffuse osteomyelitis with probably generalized septicemia.

These divisions have already been described. In type a localized to the marginal epiphyses it is wise to incise, drain and eradicate the

involved bone to establish free drainage outward for the bone itself. Simply draining the abscess might be sufficient in a low grade infection, but a virulent infection might spread rapidly in a very few hours throughout the squamous portion of the ilium. I do not advocate extensive resection in the early stages, but feel it is necessary to expose thoroughly the involved bone area so that infection in the bone will not develop pus under pressure and so that free exit of pus is secured. Later in the progress of the disease a localized resection of the involved area may be necessary. This type of localized involvement is the most favorable for treatment.

Type *b* is the diffuse type in which the patient is seriously ill. Here one must consider the general condition of the patient as well as the local condition. Starr stated that the early acute stage of inflammation with pressure from exudates is always accompanied by the clinical symptoms of pain and intense toxemia. This is also the stage of greatest danger from septicemia. "Early drainage with relief of pressure alleviates the clinical symptoms." I believe it also lessens the chance of a septicemia. In the early acute stage there will be no abscesses outside of the bone, so one must be prepared to enter the bone on the strength of one's diagnosis. The external table should be exposed by the Larghi method. It is in this type of a case that the trephining of the ilium above the acetabulum is of greatest value. It opens directly into the very seat of the infection and tends to drain both the interior of the bone and the internal iliac fossa. It can produce little harm in case the diagnosis of early osteomyelitis is wrong. This is essentially the function of the trephine operation and not, as has been advised by most authors, its employment for drainage of a recognized internal iliac abscess.

When acute osteomyelitis of the diffuse type has progressed a few days there will be in many cases a spontaneous perforation of one or the other table of the ilium with an abscess formation subperiosteal in either the internal or the external iliac fossa. This occurs by far most frequently in the internal iliac fossa. If this abscess is recognized clinically, one need not consider the trephine as a diagnostic measure. Osteomyelitis at this stage is much more extensive than in the early case, and the prognosis is more grave.

In this case it is wise not to attempt a questionably satisfactory drainage by trephining through the wing of the ilium as is commonly advised.

If the patient is extremely toxic, it might be well first merely to drain the abscess, drainage done by subperiosteal reflection of the internal table directly to the abscess in the internal iliac fossa being the method of choice. Then in a few days, when the patient is in better

physical condition, proceed with the more radical bone operation. However, if the patient's condition will tolerate it, it is better to do the radical operation at once without the preliminary drainage. The ilium should be exposed subperiosteally on both tables to the arcuate line. Resection of the wing of the ilium to the supracotyloid portion is easily and quickly done by rongeur or osteotome. The diseased bone should be removed and resection as extensive as necessary should be carried out. The disease rarely extends into the hip joint, but in such cases complete extirpation of the ilium should be done. As von Bergmann demonstrated, this can be done in patients under 13 years of age by avulsion as the cartilage of the ilium has not yet fused to the ischium and the pubis. Generally, however, in these early cases, it will be necessary only to remove the ilium to the periacetabular region. Adequate drainage is then established, regeneration of the ilium follows, and hope of a complete recovery without recurrence is good (case 1). This operation is no more shocking and no more difficult than the trephining operation. In case 1, the total time for the operation was twenty minutes.

This procedure of adequate drainage of both the abscess and the bone infection offers the patient not only the best chance for life, but a good chance for a permanent cure of the infection.

Type *c* is the diffuse type with an extensive overwhelming general infection. Whatever treatment one employs will be open to criticism. I feel certain in this group, however, that the only chance is in raising the patient's resistance by eradication of all possible local involved areas. In spite of the extremely high mortality rate in this group, the resection of the ilium is indicated in these cases.

SUBACUTE OSTEOMYELITIS OF THE ILIUM

The treatment of the subacute form of osteomyelitis of the ilium should be differentiated into the localized and the diffuse type. As the roentgenograms are of great value here, it is possible at this stage to have quite a definite idea as to the extent of damage and the location of the lesion. In the local type, local resection of the involved area is easily carried out and should be the operation of choice. In the diffuse type, one may do either a resection of both tables or a removal of the outer table and diseased bone to the inner table. The best procedure is complete eradication of both tables, and there is more certainty of a complete cure. One point which should be emphasized here is that one cannot wait for sequestration to occur as is frequently advised in subacute osteomyelitis in long bones. The problem is quite different. In osteomyelitis of long bones the continuity of the shaft must be maintained for weight-bearing. Therefore, one is very reluctant to

remove viable bone. The wing of the ilium is not essential for function and can be sacrificed if necessary. Sequestration does not occur here as in the long bones, but multiple diffuse abscesses with occasional small sequestrums are present. With complete resection all diseased bone is removed, and during regeneration in all probability a new healthy ilium will form.

CHRONIC OSTEOMYELITIS OF THE ILIUM

Chronic osteomyelitis of the ilium is a problem in itself. I have attempted removal of the outer table only, with complete saucerization of the abscesses, but a diseased area is apt to be left behind. The tremendous thickening that occurs in the ilium in chronic osteomyelitis makes it difficult to tell when one is near the inner table, and frequently there are abscess cavities under the inner table perforating into the iliac fossa. The operation of resection is not much more difficult or shocking than saucerization, and I would advocate resection of both tables. It is rarely necessary to do a complete resection in the chronic case. When the wing of the ilium to the supracotyloid region is removed, diseased bone in the body of the ilium can be eradicated by curettement and saucerization to healthy bone. The situation is ideal for saucerization, as the visceral muscle group and the gluteal group completely obliterate the cavity.

POSTOPERATIVE TREATMENT

In the greatest number of my cases I have kept the wound wide open with packs, using the Carrel-Dakin method. Thus, the wound has granulated in from the bottom. Lately I have used treatment with gauze smeared with petrolatum and have been greatly pleased with the results. Secondary closure of the wound has been done in a few of the cases with a much better resultant scar.

TECHNIC OF RESECTION OF THE ILIUM

An incision is made just below the crest of the ilium, extending from the posterior superior spine of the ilium to the anterior spine and is then extended onto the thigh lateral to the sartorius. The fascia is cut through about one-half inch below the crest, the muscles are stripped close to their attachment to the crest, and the periosteum is incised along the line of the skin incision close to the crest. By subperiosteal reflection with a sharp periosteal elevator, the gluteal muscles are stripped down to the acetabular rim. The interval between the tensor fascia femoris and the sartorius is exposed to allow retraction of the gluteal muscle mass. The anterior portion of the ilium is exposed by this subperiosteal dissection. In children the cartilaginous crest of the ilium may be detached easily with the abdominal muscle insertions still

attached to it. In older persons von Bergmann advocated chiseling off the crest of the ilium to maintain these attachments. I have found it simpler and as effective to continue the subperiosteal dissection over the crest of the ilium, separating the abdominal muscles, the latissimus dorsi, the quadratus lumborum and the spinae erectae from their insertions. When this has been completed, the abdominal contents fall away, exposing the wing of the ilium beautifully. The inner table is then stripped subperiosteally to the arcuate line of the ilium. The falling away of the abdomen makes retraction very simple (fig. 15).

In the chronic case this subperiosteal dissection will be somewhat difficult because of scarring due to perforation and involucrum, but the stripping can be done if one is patient and persistent. Hemorrhage is a negligible factor as long as one keeps the dissection beneath the periosteum.

To obtain a better exposure, the sartorius and Poupart's ligament may be stripped from the anterior superior spine.

One may then remove the ilium to the supracotyloid region *en masse* by motor saw or osteotome, if necessary back to the sacro-iliac joint. In the chronic cases, I define the extent of the lesion and remove the involved area *en masse* if possible. In the acute cases I rongeur through the ilium to note the extent of the infection, progressing through diseased bone to what is considered normal bone.

If it is felt that a patient with an internal iliac fossa abscess is too ill for such an operation, drainage of the abscess by an incision through the anterior third of the ilium with subperiosteal dissection of the internal table into the internal iliac fossa direct is advocated. Later, if the patient responds to this drainage, more radical exposure of the ilium can be performed.

If the posterior portion of the ilium or the sacro-iliac joint is chiefly involved, I have used the approach to the ilium which Smith-Petersen employs for arthrodosis of the sacro-iliac joint, but I have also resected the posterior third of the ilium. In several cases I have combined the anterior and posterior approaches for a complete exposure of the ilium. By removing the ilium posteriorly, a perfect exposure of the sacro-iliac joint is made which gives the best drainage possible for this joint.

RÉSUMÉ OF THE TWENTY-FOUR REPORTED CASES

The age incidence in my reported cases varies from 20 months to 70 years of age. Four of the patients were over 25 at the onset of their infection. Only 4 of the cases could be classified as in the acute stage and would fit better in the subacute stage, as four weeks had elapsed before I saw them. The longest period from onset of the infection until I saw the patient was twenty-five years, another was

nine years and another eight years. Eleven patients gave a definite history of trauma which bore a close relationship to the onset of the infection.

There were 18 males and 6 females in this series, ratio of 3:1.

Serious involvement of the hip joint occurred in a large proportion of the cases, bony ankylosis occurring in 9, fibrous ankylosis in 2 and pathologic dislocations in 3. The presence of the pathologic dislocations in 2 cases was apparently the result of the patient's splinting the abducted hip with the well leg, throwing the well hip into adduction, flexion and internal rotation with a resultant dislocation of the well hip. These cases led to further study with my former associate, Hart, of the mechanics of pathologic dislocation of the hip, and our study was recently published by him.

There were marked symptoms of hip irritation noted in cases 3 and 7, an abscess cavity being present in both just above the acetabulum. The patient in the first case recovered with no involvement of the joint, but in the second a stiff hip developed following an operation performed elsewhere.

In 3 cases (cases 1, 22 and 11) of acute diffuse osteomyelitis of the ilium, the hip was not involved, although marked irritation of the hip was present clinically. Radical resection or removal of the outer cortex of the ilium for drainage was employed.

In 5 other cases the hip was not involved because the lesion was local and involved the anterior third of the ilium. Two cases involved the posterior third of the ilium and invaded the sacro-iliac joint, not affecting the hip.

In my series there were 14 cases of diffuse osteomyelitis of the ilium. Ten of these patients were 14 years old or younger. One of the remaining four was 17, and in this case the infection of the ilium was a secondary lesion to a multiple osteomyelitis. Another patient was 16 years of age, and two were 15 years.

There were 10 patients with the localized type of osteomyelitis of the ilium, 9 of whom were 15 years of age or over.

These facts certainly strongly substantiate Goullioud's prepuberty and postpuberty divisions as a means of deciding whether the lesion is diffuse or local.

In my series of 24 cases the final results were seen. Two deaths occurred, one from chronic suppuration followed by amyloidosis with brain abscess as the terminal picture.

In 1 case (case 15) a recurrence of infection in the posterior third of the ilium was reported three years after operation. The patient in case 24 is in excellent health, but has a small sinus with little discharge. A total resection would have been a better procedure in her case. The patient in case 12 still has a discharging sinus and some activity, but

he is greatly improved generally. In case 18 the patient is greatly improved but still has a small sinus. In case 20 there was great improvement, but the resection was not sufficiently extensive.

Resection of the wing of the ilium was done twelve times, partial resection of the anterior or posterior third in 5 cases, removal of the outer table of the ilium accompanied by saucerization of the ilium in 4 cases, sequestrectomy and drainage in 1 and saucerization of an abscess just above the acetabulum in 2.

Seventeen of the 24 patients have been completely cured. By cured, I mean the sinuses have become obliterated, the patient's general health has returned to normal, and he is apparently well. Some of these patients have remained well for years, others for shorter periods. It is possible that they may have some recurrence, but the picture now is entirely different from that when they first consulted me.

REPORT OF CASES

CASE 1.—J. L., a boy, aged 20 months, entered the Henry Ford Hospital on Aug. 5, 1929, and was discharged September 19. Four weeks before admission a "boil" was noticed over the right thigh and was opened by the mother a few days later. Fever developed, and the child was severely ill, his temperature being 104 F. A small abscess developed over the crest of the ilium, which was lanced by the local doctor, and dark blood was obtained. The fever persisted. Roentgenograms showed a destructive process in the ilium a week before admission.

On examination the child was profoundly toxic and apprehensive. The right leg was held in abduction, flexion and external rotation, and there was marked muscle spasm. Gentle motion allowed a fair range of movement. There was marked tenderness above the trochanter and about the ilium with thickening and tenderness on palpation on the mesial side. Leukocytes were 14,500, and the temperature was 101 F.

A roentgenogram showed a mottled appearance of the ilium with a traveling acetabulum and one area which looked as though it might perforate into the hip joint. The roof of the acetabulum was displaced upward, and the head appeared partially subluxated.

The child was given fluids intravenously, and operation was performed on August 7. Incision from the anterior superior spine of the ilium to the posterior spine carried through to the bone. Subperiosteal reflection of the external table was done. There was no evidence of pus externally, but on breaking through the cortex a few drops of pus were found in the posterior angle of the ilium. The cartilaginous rim was removed from the crest after von Bergmann's method with the abdominal muscles intact. The inner cortex of the ilium was exposed, opening into a large abscess cavity filling the internal iliac fossa which drained profusely. Numerous cloacae opened from the internal table to this abscess. The ilium was removed by rongeurs, leaving only a little of the anterior and the posterior portions down to the arcuate line of the ilium.

The spongy bone left behind seemed normal. The wound was left wide open, and Carrel-Dakin's treatment instituted. Traction was applied to the hip. The child did remarkably well and was discharged on September 19, with the wound almost healed. The hip was entirely free from symptoms. On Feb. 21, 1930, the

patient reported back with a draining sinus in the posterior angle of the wound. The hip was normal clinically, and the child walked without a limp. A roentgenogram showed a suspicious area just above the acetabulum. Operation was advised, but the sinus healed shortly after this.

A letter from the patient's home doctor in January, 1931, stated that the sinus healed in a few weeks, and that the boy has been well since.

CASE 2.—F. C., a man, aged 24, entered the Henry Ford Hospital in August, 1929. Nine years before admission he fell, striking the right hip and side. They were quite painful at the time, but he was able to walk home, a distance of 2 miles. The tenderness and soreness left in a few days. Six months later, while playing hockey, he was struck over the brim of the pelvis by the puck. Immediately the area of the pelvis became blue and swollen. The physician was of the opinion that the lesion must have been present prior to the injury in order to produce such a sudden reaction. The patient was operated on; pus was found in the soft tissues,
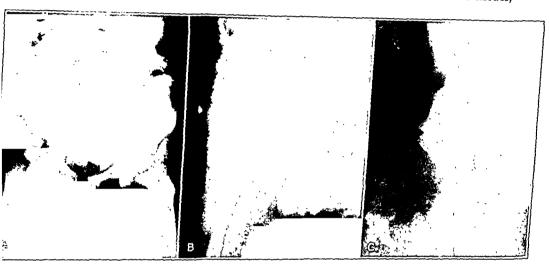
Fig. 5 (case 1).—Roentgenogram showing *A*, the typical mottled appearance seen in osteomyelitis of the ilium in the early stage. This was taken from three to four weeks after onset. Note the traveling of the acetabulum and the destruction chiefly in the periacetabular region. This is the usual site of origin of infection in the diffuse type of osteomyelitis. *B*, roentgenogram taken after operation. Extensive resection of the ilium to the body had been performed. The body portion was then given perfect drainage. Note the improved appearance of the hip joint. *C*, roentgenogram showing extensive regeneration of the ilium six months after operation. The hip joint looks quite normal. Note the improvement in the periacetabular portion of the ilium.

and the bone was found to be infected. Curettement and drainage were done. The wound healed, but would break down and discharge at intervals. The wound had been healed for as long a period as two or three months. The patient is a semiprofessional boxer, and blows in the ring precipitated drainage. The lesion interfered with his boxing and although he felt well, he wanted this corrected.

Physical examination showed an old scar over the crest of the right ilium with a small draining sinus in the inguinal region. Under the medial to the anterior superior spine of the ilium there was also an old healed sinus. Examina-

tion at that time showed marked thickening of the wing of the ilium and local tenderness. The patient was a very well built, well appearing man.

He was operated on in October, 1929. The anterior two thirds of the ilium was exposed with difficulty because of massive involucrum formation and was removed by means of an osteotome. Numerous abscesses were found throughout the ilium, one in the anterior superior spine pointing toward the sinus. Five abscesses were found in the wing of the ilium. The wound was packed wide open with gauze treated with petrolatum. No sequestrums were found, but the ilium was almost five times the normal thickness, hard and eburnated with numerous walled off abscesses.

On December 29, a secondary closure was performed which healed by primary intention.

In January, 1931, at the time of the last observation, the patient had been entirely free from difficulty since operation. He is a professional boxer and had engaged in a bout every six weeks for the past six months. Roentgenograms taken at this time showed almost complete regeneration of the ilium.
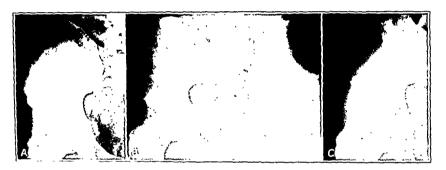
Fig. 6 (case 2).—*A*, roentgenogram showing extensive involvement of the anterior two thirds of the ilium, chronic osteomyelitis with abscess formation and perforations. Note the absence of involvement about the periacetabular region. This is the local bone lesion seen in the postpuberty stage. *B*, roentgenogram taken following resection of the diseased bone. Gas in the bowel causes the apparent rarefaction in the remaining portion of the ilium. Note how sharply one may resect out the involved area in chronic localized osteomyelitis of the ilium. *C*, roentgenogram showing regeneration following resection one year after operation.

CASE 3.—R. M., aged 21, a college student, entered the University Hospital in September, 1926, with pain in the right hip of two weeks' duration. There was a recurrence of symptoms in February, 1927, of one month's duration, but severe enough to take the patient out of school for a semester. He had another attack of two days' duration last summer. The last attack began on March 22, 1928, with a painful hip. The leg was held in a position of abduction, flexion and external rotation with muscle spasm and limitation of motion in all directions. The temperature on admission ranged from 99.6 to 102.2 F. The leukocyte count was 16,000, and there were 4,800,000 red blood cells. The hemoglobin was 87 per cent and polymorphonuclears 78 per cent.

Stereoscopic studies of the right side of the pelvis demonstrated several well defined areas of rarefaction with a sclerosed border in the lower part of the ilium just above the acetabulum. No involvement of the hip was noted.

Operation was performed on April 2, and the anterolateral approach was used. The ilium was exposed and pus was found between the gluteus medius and tensor fascia. The pus was entirely extracapsular and came from the ilium through a small opening just above the acetabulum. The cortex of bone was removed by means of an osteotome, and the bone was eburnated. A cavity filled with pus was exposed. This cavity led into two deeper cavities filled with pus. These cavities were saucerized, Carrel-Dakin tubes inserted, and the wound left wide open for drainage. Bacteriologic examination showed Staphylococcus aureus. The pathologic report was "purulent osteomyelitis without tubercles."

The patient's convalescence was uneventful; the wound remained clean, healed rapidly, and the symptoms in the hip disappeared completely. He was discharged from the hospital with a nonweight-bearing caliper on April 27.

On Feb. 8, 1929, at the time of the last observation, the patient had been free from all symptoms, had gained 20 pounds (9 Kg.) and his general health was excellent. There was a small pinpoint sinus in the scar, from which there was no drainage.

Fig. 7 (case 3).—*A,* roentgenogram showing localized abscess in the periacetabular region not involving the hip joint. *B,* roentgenogram made after operation. Saucerization of the abscesses was done without involving the acetabulum. *C,* roentgenogram taken after clinical cure was obtained. Note the apparent bone obliteration of the cavities.

CASE 4.—C. E., aged 15, entered the University of Michigan Hospital on Nov. 23, 1923, with chronic suppuration, marked deformities of both hips and draining sinuses. The onset was a year previous to admission. There was pain in the left hip and anterior aspect of the thigh. The patient had a high fever, was acutely ill and was kept in bed. On December 3, he was sent to a hospital at Lansing, Michigan, where a diagnosis of "typhoid fever" was made. He was in the hospital six weeks, swelling in the hips, knees and the ankles developing; the left shoulder became sore, and the left hip assumed a flexion, abduction and external rotation deformity. The right hip was in a position of adduction, flexion and internal rotation. Six months after onset an abscess in Scarpa's triangle developed on the left side, which ruptured spontaneously and which has drained ever since. A few weeks later a similar abscess developed on the right thigh and ruptured; it was still draining on the patient's admission to the University Hospital.

Physical examination showed an anemic scrawny child. A hard mass was felt in both lower abdominal quadrants in the region of the internal iliac fossa. This mass was not fluctuant. There were iliac abscesses. The left shoulder was limited in abduction especially, but in all motions somewhat. The right hip was held in abduction, flexion and internal rotation. There was a flexion contracture of the knee. There was marked limitation of motion of the hip in all directions. The left hip was ankylosed solidly in abduction, flexion and external rotation. There was a flexion contracture of the left knee.

The patient was given fluids and two transfusions.

On Dec. 18, 1923, operation was performed, and the abscesses in left Scarpa's triangle incised and drained. On Jan. 12, 1924, the right anterior abscess was drained. On January 15, the left sacro-iliac joint was drained by Smith-Petersen's approach.

Roentgenograms showed pathologic dislocation of the right hip with absence of the head. The left hip showed bony ankylosis.

The patient's general condition was not good at any time, and it was felt that he would not stand extensive operation until he could be put in better physical condition. He showed clinical evidence of amyloidosis. The urine contained hyaline and granular casts, 200 white blood cells, many cocci and a few bacilli. Numerous transfusions were given and incision and drainage of the abscesses performed several times.

On July 3, the patient appeared in fair condition for him, so an attempt at resection of the ilium was made. The incision under the crest was used; the ilium was exposed and found to be filled with abscesses. The outer table was removed and Carrel-Dakin's tubes inserted.

On August 17, the patient died of symptoms corresponding to those of brain abscess.

CASE 5.—C. H., aged 14, entered University of Michigan Hospital on May 13, 1924. The onset of his condition was the year previous with pain in the right hip, which was severe, confining him to bed. A week later the leg was in flexion deformity. The patient was taken to a hospital, where he remained for seven months. The right hip discharged spontaneously, and there had been a discharging sinus there since. Two months before admission, the opposite hip became painful and finally opened spontaneously, leaving a discharging sinus.

Physical examination showed the right hip in a position of marked external rotation and abduction, and the left hip in a position of adduction and flexion, with limitation of motion. There were no areas of tenderness over the femoral shaft. There was a sinus in the posterior aspect of the left thigh and two sinuses in the upper third of the femur. The right hip was ankylosed in a position of 60 degrees abduction and 15 degrees flexion.

The diagnosis was pathologic dislocation of the left hip, osteomyelitis of the trochanter and upper third of the left femur and osteomyelitis of the right wing of the ilium with extensive involvement of the acetabulum.

On May 17, the ilium was incised and drained, and numerous small sequestrums were removed. Bacteriologic examination showed staphylococcus with slight hemolytic tendencies.

On June 7, saucerization was done.

On June 21, saucerization of the femur was done followed by dislocation that afternoon. Dislocation occurred after this operation for osteomyelitis of the trochanter, very probably influenced in part by loss of the gluteus muscles and abduction of the opposite leg.

On December 3, Steinman pin traction was used to pull the left leg down for reduction of the dislocated hip.

On December 20, the pin was removed because of infection.

On Aug. 5, 1926, the wounds were practically healed. The patient was in good enough condition so that osteotomy could be considered to correct the deformity of the right hip.

On September 8, the patient returned to the hospital with an abscess, which was drained.

On March 3, 1927, an abscess over the right trochanter was incised and drained.

On April 1, the patient returned with a temperature of 101.8 F., *pulse rate 90, respirations 22, a flare-up in the right lower quadrant just above the anterior superior spine and an abscess in the lower lumbar region.* At this time the urine showed albumin 4 +, casts and white blood cells. There were 40,000 leukocytes.

On April 4, an abscess in the lumbar region was incised and drained.

On Feb. 21, 1928, osteotomy was done to correct the deformity of the right hip.
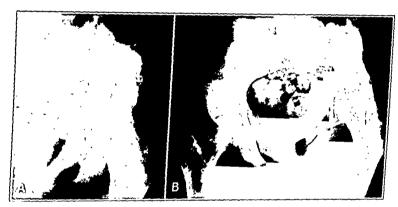
Fig. 8 (case 6).—*A*, roentgenogram showing subacute osteomyelitis of the ilium of the diffuse type with invasion of the hip joint. Note the mottling with areas of increased density intermingled with rarefied areas. *B*, roentgenogram taken after operation; partial resection and excision of the outer table was done. Numerous sequestrums were found in the supra-acetabular portions of the body of the ilium.

On April 4, suppurative parotitis developed.

Death occurred on April 8 from pyemia.

CASE 6.—L. L., aged 13, entered the University of Michigan Hospital on Oct. 6, 1924. The condition began with a painful left hip on September 4, following a severe cold. On October 8, incision and drainage was performed and was repeated on November 5, November 20, April 23, 1925, June 19, and September 15. On September 22, incision and drainage of the clavicle was performed; on May 19, 1926, incision and drainage of an abscess of the cheek; on July 9, incision and drainage of an abscess in the left axilla and right thigh, on December 24, incision and drainage of the right humerus and on Nov. 5, 1927, incision and drainage.

On December 2, iliectomy was performed, the usual incision being used. There was a large abscess between the iliacus and internal table, penetrating the iliacus fibers. There were two large sequestrums in the abscess and a hole in the anterior portion of the ilium communicating with the abscess. The abscess also followed the sinus tract under the ilium to point at the sciatic notch. Iliectomy was per-

formed, the incision following the crest of the ilium, and the ilium was explored subperiostially, stripping the gluteal and abdominal muscles from the crest. The ilium was removed almost to the pubic ramus. A sinus which communicated with the abscess in the iliacus muscle was found just below the sciatic notch.

The pathologic examination showed chronic purulent osteomyelitis.

On July 11, 1929, the patient returned with an abscess over the posterior end of the scar over the left ilium. The abscess was healing satisfactorily.

In January, 1931, when the patient was last seen, she had had no further recurrence of the difficulty in the ilium. However, she returned to the hospital in January, 1930, with a recurrence of osteomyelitis in the clavicle.

CASE 7.—D. D., aged 23, entered the University of Michigan Hospital on Dec. 30, 1926, with history of an acute osteomyelitis of the left tibia at 15 years of age. While the patient was on a geological survey in California a month before entrance to the hospital, a severe pain referred to the left sacro-iliac joint developed. He was treated in a hospital in California for acute sacro-iliac strain. After four weeks he was becoming progressively worse, so entered the University
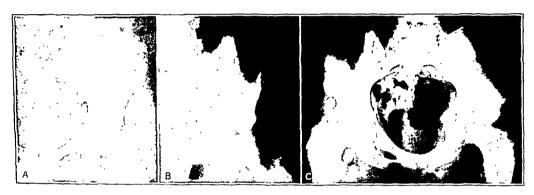
Fig. 9 (case 7).—*A*, roentgenogram showing a rarefied area in the ilium above the acetabulum but not invading the hip. The patient was operated on elsewhere by trephine. *B* shows apparent perforation into the acetabulum; osteoporosis of the head of the femur and narrowing of the joint cavity. *C* shows more marked evidence of involvement of the hip. The rarefied area is still prominent and not tending to close by bone proliferation.

Hospital at Ann Arbor. At the time of admission there was a large fluctuating abscess pointing just below Poupart's ligament medial to the anterior superior spine of the ilium. There was marked limitation of motion of the left hip associated with muscle spasm. A flexion contracture was present. The hip, on gentle movements, could be moved fairly freely. The patient was acutely ill and had a temperature of 100.6 F.; pulse rate, 120; respirations, 24, and leukocytosis.

A roentgenogram showed an area the size of a nickel in the ilium just above the acetabulum but not perforating it, which seemed to be the focus of the difficulty. A diagnosis of osteomyelitis of the ilium was made. My intentions at first were to drain the anterior abscess and then drain the ilium by a trephine operation, but the patient was too toxic for an extensive operation.

The abscess, which was very extensive, was drained through an incision over the crest of the ilium anteriorly on the visceral side of the ilium. The internal table of the ilium was felt with the fingers, and no perforation could be found. It was thought wise to stop at this point. Following the operation, the infection in the

hip joint subsided completely, but the patient had symptoms of sciatic irritation with hyperesthesia of the left great toe. Repeated roentgenograms showed the suspicious rarefied area in the ilium filling in with lime salts. The patient recovered completely.

He returned in January, 1927, with another large abscess in the internal iliac fossa. The ilium still looked normal. The abscess was drained anteriorly, and extensive exploration of the visceral side of the ilium showed no definite site of the infection. Staphylococcus aureus and albus were found.

On May 8, 1928, a third iliac abscess formed and was drained. This time the anterior border of the ilium was dissected free subperiostially, and an excellent view of the entire internal table of the ilium showed no evidence of perforation or active involvement. The sacro-iliac joint appeared normal roentgenographically and clinically.

The patient was free from symptoms following this until 1929, when he was injured in California and pain again developed in the left hip. He was treated by one of the leading orthopedists there. The previously described area of decreased density was noted in the ilium, a trephine operation was performed, and a cavity containing pus was found. Following this operation the wound healed, but a fibrous ankylosis of the hip resulted. There has been no flare-up of the infection since.

Case 8.—M. R., aged 17, entered the University of Michigan Hospital on July 8, 1927. He dated December, 1924, as the time of onset of his condition. The primary trouble was in the right tibia, later in the femur, and in 1926 the left ilium became involved. The patient gave a history of chills, fever, redness and tenderness over the right tibia, and pain in both knees.

There was marked tenderness over the crest of the ilium with a discharging sinus at the crest of the left ilium.

Roentgen examination showed a defect of the ilium on the left side in the region of the superior iliac spine.

On September 26, an incision 5 inches (12.7 cm.) long was made along the crest of the left ilium from the anterior superior spine posteriorly. An abscess cavity was found which centered around a perforated hole in the ring of the ilium, the hole being 3 cm. in diameter. The crest above this was removed, the scar tissue excised, and the wound loosely closed. The femur and tibia were also drained.

In January, 1929, the patient reported back to the hospital. The ilium was completely healed.

The pathologic report showed active purulent osteomyelitis.

Case 9.—P. S., a youth, aged 18, was admitted to the University of Michigan Hospital on Feb. 8, 1929, with a condition which began three years previous to admission, the result of a misstep. His right foot doubled up under him, and difficulty in walking followed. Four days later he had an elevated temperature, and the doctor diagnosed typhoid fever, but the chief complaint was in the right hip. The patient was in bed six months, following which he got around but he had pain in the right hip, and the leg became shorter. One year before admission a sinus developed over the anterior aspect of the hip, and this had drained since its appearance.

Physical examination showed no motion in the right hip, and it was ankylosed in a position of 40 degrees adduction and 60 degrees flexion. There was no pain. There was a draining sinus on the anterior aspect of the joint. There was ½ inch (1.27 cm.) true shortening and 4 inches (10.16 cm.) apparent shortening.

On February 14, operation was performed. From four to five perforating holes were found in the wing of the ilium with tissue formation extending through to the iliacus; one large cavity led directly to the iliacus and drained into a sinus in the groin. The ilium was removed from just above the pubis to the posterior one-third.

On March 6, secondary closure was done.

Pathologic examination showed purulent osteomyelitis, very active osteomyelitis with marked necrosis of the bone and many foreign giant cells.

On June 3, the patient returned with excellent results except for two small sinuses at the center of the wound, the rest being healed. There was definite regeneration of tissue.

On November 16, there was complete healing.

CASE 10.—E. D., aged 17, was admitted to the University of Michigan Hospital, on Aug. 8, 1927. On January 1, the right ankle was slightly reddened and swollen. Two weeks later there was swelling of the right knee and pain in the right hip on

Fig. 10 (case 10).—*A*, roentgenogram showing involvement chiefly about the acetabulum and anterior third of the ilium with partial ankylosis of the hip. *B*, roentgenogram taken some months after operation. Note area of resection with regeneration of bone.

walking, associated with chills and fever. The patient was in bed for two months, and there was a loss of weight of 30 pounds (13.6 Kg.). The patient entered the hospital walking with a cane, complaining of pain in the knee.

The right hip was held in 35 degrees flexion deformity, neutral in position, and 1 inch shortening. The trochanter was 1 inch above Nelaton's line, with some atrophy; there was ankylosis of the hip, and the knee was normal.

The roentgenograms showed a destructive process which had destroyed the head of the femur and corresponding surface of the acetabulum. The process had extended well into the ilium.

Operation was performed on August 25. There was a large involucrum formation lateral to the anterior superior spine of the ilium in which there was a large amount of pus and a few partially separated sequestrums. The involucrum was removed, as was the outer cortex of the ilium down to the acetabulum. Sauceriza-tion of the outer cortex of the ilium was performed.

The pathologic report was active chronic purulent osteomyelitis. The bacteriologic report showed Staphylococcus aureus.

In November the patient had some pain in the right thigh on motion, but by December 30 he was free from symptoms. There was no tenderness over the pelvis or femur, and there were no sinuses.

Case 11.—J. M., aged 14, entered the University of Michigan Hospital on July 30, 1927. One year before admission, he had fallen from a tree; since then he had had pain in the right hip. The day before admission pain and swelling developed in the left elbow.

Physical examination showed a sinus in the anterolateral surface of the right femur with marked muscle spasm and fixation of the hip joint in abduction, flexion and external rotation. Movements could be carried through almost normal range if carefully done. There was swelling over the ilium with marked thick-
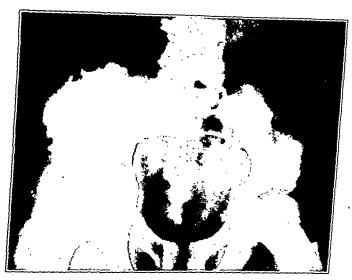
Fig. 11 (case 11).—Roentgenogram showing typical chronic diffuse osteomyelitis of the ilium. Note the tremendous bone proliferation and the areas of marked density with rarefied areas spread throughout. The sacro-iliac joint also is involved. Resection is indicated in this type of case though the external table was excised.

ening of the bone. The left elbow showed synovial thickening, increased fluid, tenderness and limitation of motion.

On September 27, operation was performed on the right ilium, the external table being exposed only by incision under the crest of the ilium and subperiosteal resection. This was somewhat difficult because of dense marked involucrum formation extending in knobs well away from the ilium proper. There were many abscesses throughout the bone and an abscess in the soft tissue just above the acetabulum. The anterior third of the outer table with the involucrum was removed, and the wound was treated with Carrel-Dakin technic. The hip cleared up quickly, all symptoms disappearing, and the elbow improved completely simply by aspiration.

On July 19, 1928, a sinus persisted over the ilium, and a recent flare-up brought the boy back to the hospital. The ilium was explored subperiosteally by incision under the crest. The outer table had reformed with dense involucrum and numerous

abscess cavities throughout. In the posterior third of the ilium between the two cortical layers a large pus cavity was found containing several small sequestrums. No abscesses pointing toward the visceral side could be seen. Bone was removed almost to the internal table of the ilium.

On April 9, 1929, the patient returned to the hospital and at this time the hip was entirely normal. There was a slightly draining sinus over the inguinal region, which was symptomless.

CASE 12.—F. L., aged 16, was admitted to the University of Michigan Hospital on March 30, 1929. A diagnosis of chronic osteomyelitis of the right hip and ilium, pathologic dislocation of the right hip and acute thrombophlebitis of the left leg was made. The onset was three years prior to admission, the patient having been injured while playing football. There was pain in the hip, and the patient walked with a limp. In May, 1928, he had a high fever and severe pain in both hips. In September, 1928, a sinus appeared in the right thigh, and in December, 1928, there was drainage of the right hip.

Physical examination showed an acutely ill, markedly emaciated patient with decubitus over the back, scapula, sacrum and calf of the left leg. The right elbow was slightly fixed. There was a long scar over the right thigh with a draining sinus at the lower end from which greenish-yellow purulent pus flowed. There were marked limitation of motion of the hips in all directions, definite fluctuation in the thigh and 1 inch (2.5 cm.) shortening of the right leg.

A roentgenogram showed a marked destructive process including the head and neck of the right femur and the right ilium, dislocation of the head of the femur and sacro-iliac synchondrosis involvement on the right.

On May 23, incision and drainage of the iliac abscess was performed by Dr. Hart. The abscess occupied the right iliac fossa beneath the iliac muscle. The wound was packed. Iliectomy was advised later.

On June 1, the wing of the ilium was removed from the anterior superior spine to the sacro-iliac synchondrosis behind.

Pathologic examination revealed very active chronic purulent osteomyelitis.

At the last report the abscess had healed.

CASE 13.—H. E., aged 18, entered the University of Michigan Hospital on Aug. 20, 1928. At the age of 7 the patient fell and dislocated the left hip. Pain continued for a year, and limping resulted. Operation was performed elsewhere a year before admission, and two draining sinuses were present on admission.

Physical examination showed the hip held in a position of 35 degrees adduction, 35 degrees flexion and slight internal rotation. There was apparent shortening of 3 inches (7.6 cm.) and the actual shortening was 1½ inches (3.8 cm.). There was a limitation of motion of about 10 degrees forward and lateral, and about 20 degrees internal rotation. Urinalysis at that time showed albumin 1 +, hemoglobin 76 per cent and leukocytes 23,000.

Iliectomy was performed on Sept. 4, 1929, by Dr. Hart. The wing of the ilium was excised. There was marked thickening, several small perforations on the visceral side and no subiliac abscesses.

Pathologic examination showed pyogenic granulation tissue containing necrotic bone, chronic osteomyelitis and osteitis. Bacteriologic culture revealed B. coli.

On October 12, there was secondary closure.

The last report showed that the wound was healed and the patient apparently was cured.

CASE 14.—C. H., aged 16, entered the University of Michigan Hospital on May 7, 1928; two years before entrance an attack of pain and swelling in the left

hip and spine developed; he was placed in a spica and kept in bed for two months. He has no remembrance of fever. The pain subsided, the cast was removed, and the patient was symptomless until three months before admission. At that time a sinus which has since drained developed. At no time were there pain, swelling or fever, and there were no symptoms in the hip.

Physical examination showed a draining sinus in the region of the left sacro-iliac joint and thickening of the ilium posteriorly, but no evidence of involvement of the hip.

A roentgenogram showed sequestration in a perforated cavity in the ilium. The sacro-iliac joint appeared involved with sclerosis.

Operation was performed on June 7. Incision was made over the posterior two thirds of the crest of the ilium to the posterior superior spine and continued down the trochanter. The gluteal muscles were separated from the crest of the ilium down to the junction of the inferior spine and sacrum. Incision was then carried through the gluteus maximus. A sequestrum was found lodged in the sinus, and this was removed. The sinus tract could not be traced to the ilium, and the exposed portion of the ilium and outer cortex appeared normal. A window was
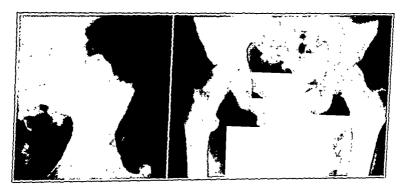
Fig. 12 (case 14).—Roentgenograms showing involvement of the posterior third of the ilium with invasion into the sacro-iliac joint.

cut out of the ilium to the sacro-iliac joint and a very thick cartilage found. There was no pus. The window was removed and a small drain inserted.

Pathologic examination of a specimen of necrotic hyaline cartilage showed no actual infection.

A roentgenogram on Sept. 11, 1929, showed an operative defect in the left wing of the ilium, increased calcification and involvement of the left sacro-iliac joint, but no evidence of activity.

On February 23, the patient returned with a draining sinus. A roentgenogram showed extension of the process in the ilium.

On March 1, iliectomy was performed. Incision was made along the crest of the ilium and posterior two-thirds carried through the gluteus maximus fibers to the trochanter. The ilium was exposed, and a large opening found in the posterior lower portion just in front of the greater sciatic notch. This was filled with pus and granulation tissue, and several sequestrums of large size were removed from this opening. The epiphysis of the crest was dissected free with the abdominal muscle insertions, and the inner table of the ilium was exposed. With an osteotome, the wing of the ilium was removed, exposing a large abscess cavity in the inner table, which had broken through and led between the periosteum and inner table of the ilium. The cavity in the ilium itself was ¾ inch (1.9 cm.)

long and ½ inch (1.27 cm.) wide. The ilium was removed from the posterior one-third to the sacro-iliac joint. This joint was opened. It showed no pus, but there was definite thickening and fibrosis.

On March 22, secondary closure of the wound was done. Bacteriologic examination showed Staphylococcus aureus. Pathologic examination showed degenerating cartilage, pyogenic granulation tissue, numerous foreign body giant cells and very active chronic purulent osteomyelitis.

The last report, made on September 10, showed that there had been a history of draining sinus since the patient left the hospital. At one time a small sequestrum was removed. There was one attack of high temperature, breaking down of the wound, and extensive drainage of pus followed by complete relief. The patient was apparently cured.

CASE 15.—L. S., a woman, aged 29, entered the University of Michigan Hospital in August, 1926. The onset was six months before entrance to the hospital. There was swelling over the posterior aspect of the thigh and pain on walking. Incision and drainage were employed elsewhere, and the patient was confined to bed for ten weeks. Following this, there had been a discharging sinus with occasional spicules of bone.

Physical examination showed a sinus in the posterior aspect of the thigh above the greater trochanter. The hip was normal clinically.

Operation was performed on August 30, by Dr. Hensel. There was a destructive osteomyelitis with attempted repair, involving the upper third of the anterior two thirds of the ilium with multiple abscess formation and involucrum in the bone. The ilium was about 2 inches (5 cm.) thick at the crest. Both tables of the ilium were exposed by subperiosteal reflection, and the diseased area was completely resected. The wound was kept open, and Carrel-Dakin treatment was instituted.

In January, 1927, the wound was reported completely healed and the patient apparently cured.

CASE 16.—E. N., a man, aged 70, entered the University of Michigan Hospital on Feb. 17, 1926. He had previously received a penetrating wound over the right ilium while cutting a board with a circular saw. The wound never quite healed, and a draining sinus had persisted.

Physical examination showed a discharging sinus over the lateral surface of the right ilium. There were slight limitation of motion and pain in the right hip.

A roentgenogram showed a perforation of the ilium 1 inch above the acetabulum about 1½ inches in diameter.

Operation was performed on April 26, by Dr. Visick. An incision parallel to the gluteal fibers led directly to a large abscess cavity in the wing of the ilium, filled with granulation tissue, pus and a small sequestrum. A large piece of wood, 1½ inches in length and 1 inch in width, was removed. The cavity was curetted. The wound was kept open and treated by Carrel-Dakin technic.

In December, 1927, the patient returned with the wound completely healed.

CASE 17.—M. B., a woman, aged 21, entered the University of Michigan Hospital on Feb. 23, 1927. Two and a half years before admission, pain on walking developed in the hip. An abscess formed, which was drained by the home physician, and the patient was confined to bed for three months. There had been a persistent sinus, and she had had four subsequent similar attacks of pain followed by an abscess which drained spontaneously.

Physical examination showed a small draining sinus in the left inguinal region near the anterior spine apparently from an internal iliac fossa abscess. The hip joint was normal.

A roentgenogram showed an irregular area of bone absorption in the wing of the left ilium posterior to the anterior superior spine with osteosclerosis surrounding it.

Operation was performed on March 5, by Dr. Darling. An incision was made over the crest of the left ilium, and the ilium was explored by subperiosteal reflection. A sequestrum, 1.5 cm. in diameter, was removed from between the tables of the ilium. Saucerization of the cavity was done. The pathologic report showed pyogenic granulation tissue, active purulent inflammation and fragments of necrotic bone. In one portion granulation tissue showed many tubercles.

A diagnosis of pyogenic and tuberculous infection was made.

On July 7, 1927, the patient reported back to the hospital with the abscess completely healed and apparently cured.

CASE 18.—J. H., a youth, aged 16, entered the University of Michigan Hospital in April, 1929. There had been an injury to the right hip in November, 1918. Three weeks later an acute respiratory infection developed and was followed a week later by severe painful swelling in the right hip. The patient's temperature

Fig. 13.—Photograph of a partial resection to demonstrate the areas of perforation commonly seen in osteomyelitis of the ilium.

was 104 F., and he had chills. A little later osteomyelitis of the left tibia and humerus developed. Eight weeks later he was taken to a reputable clinic where a diagnosis of tuberculosis was made. He was advised as to heliotherapy and antituberculous regimen.

Physical examination showed the right hip held in flexion and slight adduction, and there was marked local tenderness over the right ilium. An indurated tender mass could be palpated in the right lower quadrant. There were ¾ inch (1.9 cm.) actual shortening and 1¼ inches (3.1 cm.) apparent shortening of the right leg. There were marked limitation of motion of the right hip and almost a complete fibrous ankylosis; osteomyelitis of the tibia and humerus was also present.

Operation on the ilium was performed on May 8, a subperiosteal exposure of both tables being used. The ilium was markedly thickened with numerous superficial abscesses in the outer table. The inner table had two perforations with internal iliac abscesses filled with necrotic bone and pus. The wing of the ilium was resected from the upper margin of the hip joint. The wound was packed open.

On June 10, a secondary closure was performed.

On October 21, the patient returned to the hospital in excellent general health, walking with crutches. There was a slight draining sinus over the ilium.

Case 19.—J. L., a youth, aged 20, entered the University of Michigan Hospital in October, 1924. The onset was eight years before admission. The patient injured his hip while skating, and the following day pain in the abdomen and left hip developed, with high fever and delirium for two or three weeks. This was diagnosed "typhoid fever." An abscess pointed in the left groin and ruptured spontaneously. Several other sinuses appeared. There has been chronic suppuration for the past eight years.

Fig. 14.—Roentgenogram showing chronic osteomyelitis of the ilium of twenty-five years' duration. Note the bony ankylosis of both the hip and the sacro-iliac joint, also the density of the body of the ilium. Several very extensive abscess cavities with pus under pressure were found here. Chronic diffuse osteomyelitis of the ilium.

Physical examination showed a sinus over the sacro-iliac joint posteriorly and another draining sinus distal and medial to the anterior superior spine of the ilium. The hip was ankylosed in adduction, flexion and external rotation.

Operation was performed on October 29. A lateral incision was made through the gluteus medius fibers, the anterior half of the ilium being exposed. A large perforation through both wings of the ilium which connected directly with an abscess in the internal iliac fossa was found. Curettement was done, and Carrel-Dakin treatment was instituted. The wound did not heal, and discharge continued.

Another operation was performed on Jan. 31, 1925. The ilium was exposed subperiosteally by an incision beneath the crest and stripping of the periosteum off both tables. An abscess in the internal iliac fossa had been insufficiently drained at the previous operation through the spontaneous perforation. The sartorius muscle and Poupart's ligament were dissected free from the anterior spine of the ilium. The anterior two thirds of the ilium from a point above the acetabulum was resected. This gave an excellent exposure of the greatly thickened ilium posteriorly. Between the two tables numerous sequestrums which extended back almost to the sacro-iliac joint were found. The sequestrums and the outer

Fig. 15.—A schematic drawing illustrating the incision employed and emphasizing how prominently the ilium protrudes through the wound after subperiosteal resection of the muscles. In this type of case resection of the wing is done. Poupart's ligament can be reflected also from the spine of the ilium and one may remove the bone from the superior ramus of the pubis back to the sacro-iliac joint. The approach is termed Larghi's by Bergmann.

table were removed. The wound was left wide open, and Carrel-Dakin treatment was employed.

In February, 1929, when the patient was last seen four years after operation, he reported that he had had no difficulty since six months after operation and had been working daily. The hip fixed in 80 degrees flexion and 10 degrees adduction, not a bad position for function. He had been walking with a lift on his shoe. Osteotomy was advised but refused.

CASE 20.—F. A. S., a man, aged 43, entered the University of Michigan Hospital on July 18, 1924. The onset of his condition was three years before admission. He had his appendix removed. A year before admission an abscess developed and this was drained in October. The abscess was apparently pelvic in nature, pointing in the inguinal region. It drained for six weeks, and the sinus had not healed since drainage.

Physical examination showed a discharging sinus in the right iliac region just below the crest of the ilium at the outer edge of the inguinal ligament. There were limitation of motion of the hip and pain on motion.

A roentgenogram on July 21 showed bone necrosis in the upper portion of the right ilium. There were no sequestrums. There was a bone defect in the upper portion of the right ilium of considerable size, the lower end of which was greatly thickened.

Operation was performed on June 8, 1925. A triangular area was removed from the ilium. The process appeared to extend below the area removed and seemed to be sclerotic bone.

On April 8, 1926, the sinus was almost healed. Respiratory infection contraindicated radical surgical procedures at that time. The patient was requested to return for extensive operation in case the sinus did not remain healed.

CASE 21.—N. L., a man, aged 31, entered the University of Michigan Hospital on Jan. 7, 1926; he had pain in the right hip and abdomen and a sinus in the anterior part of the hip. The onset was five years before entrance following a gunshot wound. Operation for removal of the bullet was performed in May, 1920. The patient had had pain in the hip since that time. Two other operations were performed for incision and drainage of the abscess.

Physical examination showed an abscess on the left side of the second and third lumbar vertebrae. The hip joint was freely movable but painful. There were 4 inches (10.16 cm.) apparent shortening and 3 inches (7.6 cm.) true shortening. Abduction was limited, and there was some atrophy of the right leg. There were numerous operative scars on the right buttock and hip and a sinus in the anterior portion of the groin.

Operation was performed on January 15. The sacro-iliac joint was exposed. Gross appearance of the joint was that of infection, but no frank pus was seen.

The pathologic report showed chronic osteomyelitis.

On March 30, a second operation was performed. A rectangular section of the entire thickness of the ilium was removed, and a chronic abscess of the mesial side of the ilium embedded in the iliacus muscle was drained. The patient had a prolonged convalescence with a discharging sinus for months following operation.

On April 19, 1927, the patient returned to the hospital with the wounds entirely healed. Movement in the hip was slightly limited, especially abduction. There was 3 inches shortening of the leg.

CASE 22.—This case is reported by the courtesy of Dr. James R. Tillotson, Lima, Ohio. Roentgenograms were seen and resection or removal of the outer table advised by Dr. Badgley in January, 1928.

V. M. S., a girl, aged 12, had had a chill on July 29, 1927, followed by high temperature which continued over a period of two weeks. There was considerable swelling in the right hip extending down to the knee. There was severe pain in the hip. The local physician made a diagnosis of "muscular rheumatism." Heat was applied, and the patient was confined to bed until September 11. She was up part of the time in September and was confined to bed again in October. She was up about three weeks in November, became worse, and was again confined to bed. Dr. Tillotson and Dr. Martin were called in for consultation in August, 1927. At that time there was swelling about the hip but no redness. There was acute pain

in the hip, and the patient had a fever. On Jan. 6, 1928, she was admitted to the Tima City Hospital under the care of Dr. Tillotson.

Roentgenograms taken on Aug. 15, 1927, showed some rarefaction of the ilium, especially about the right acetabulum, and also some rarefaction at the symphysis pubis. The flat portion of the ilium showed little or no change.

Roentgenograms in October, 1927, showed the entire ilium porous, also the ramus of the pubis; at the symphysis it looks as if it were about to separate from the opposite side. There was breaking through of the periosteum in several places.

Roentgenograms in November, 1927, showed no progress of the disease.

Roentgenograms on Jan. 11, 1928, showed a marked osteoporosis of the entire right ilium. The pubis appeared about the same as before. At that time both Wassermann and Pirquet tests were negative.

The diagnosis was osteomyelitis.

Operation was performed on February 28, the Smith-Petersen incision and subperiosteal dissection from the crest of the ilium to the acetabulum being used. The outer table of bone was removed, 3 by 4 inches. It was drained anteriorly, and an abscess in the mesial aspect of the right thigh in the upper third was incised.

The patient was discharged from the hospital on May 6. There was no drainage. At this time patient was walking, and there was no impairment of motion.

At operation there was seen a honeycomb condition of bone with pockets of pus, staphylococcus and pneumococcus.

CASE 23.—J. X., a man, aged 22, entered the University of Michigan Hospital on April 18, 1928. At the age of 16, following a fall on the right hip, there was sudden onset of the condition. There were pain and limitation of motion in the hip, high temperature and abscess formation with incision and drainage, followed by persistent sinuses. The patient was hospitalized for eighteen months. Since that time he had had an ankylosed hip in position of marked abduction, external rotation and flexion.

Physical examination showed the hip ankylosed in external rotation, 45 degrees abduction and 30 degrees flexion. There was a draining sinus posterior to the right sacro-iliac joint and numerous healed scars over both the right and left hips. Urinalysis at this time showed albumin 4 + with many red and white blood cells.

The roentgenograms showed bony ankylosis of the hip in the deformity noted. There were marked thickening of the upper portion of the ilium and evidence of bony proliferation. There was an area of rarefaction with a shadow of increased density in this area suggesting a sequestrum.

Operation was performed on April 21. The ilium was exposed by subperiosteal reflection on the mesial and external sides. A large abscess cavity on the mesial side of the ilium which was in the substance of the iliacus muscle and extended down deeply below the pubic ramus was explored. Several areas of perforation were found in the wing of the ilium. The wing of the ilium from the anterior superior spine to the sacro-iliac joint was removed to just above the acetabulum. Several small sequestrums were found in the cavities in the ilium.

The bacteriologic report showed Staphylococcus aureus.

The patient returned on December 27, and at that time general condition was excellent.

CASE 24.—F. G., a woman, aged 35, entered the Henry Ford Hospital in March, 1929. The onset of her condition was at the age of 10 years with "typhoid fever." The patient was acutely ill with pain in the left hip. The hip assumed the deformity of abduction, external rotation and flexion, which was corrected by a plaster spica. The patient was confined to bed for weeks. After the spica was

removed, the hip was ankylosed. In 1907, a "curettement" of the ilium was done. In 1920, the flexion contracture of the hip was corrected by an osteotomy. In 1928, an abscess developed over the left hip and drained spontaneously. Six months before admission pain in the left hip and a sinus in the left labium developed.

Physical examination showed healed operative scar over the left ilium with loss of normal contour of the ilium. There was an old operative healed scar over the trochanter. There was a sinus in the left labium majora which on probing drained toward the pubis.

Roentgenograms showed evidence of partial resection of the crest of the ilium, marked thickening and sclerosis of the remaining portion with an area of decreased density above the acetabulum surrounded by eburnated bone, very probably abscess cavities. Both the sacro-iliac and the hip joint showed bony ankylosis. Injection into the sinus of iodized poppy seed oil 40 per cent led to the femur where there was an old osteomyelitis.

Operation was performed on March 18. Subperiosteal reflection of the external table of the ilium was performed. Dense eburnated bone was exposed throughout the wing of the ilium to the acetabulum, and thick cortical bone and involucrum were removed. After about an inch in thickness had been removed, several large cavities filled with pus were exposed under pressure just above the acetabulum and extended back toward the sacro-iliac joint. No sequestrums were found. Resection was not done as saucerization seemed complete.

The bacteriologic report showed Staphylococcus aureus.

In May, 1930, the patient reported back in excellent health. The sinus in the labium majora was healed. There was a slightly discharging sinus over the outer aspect of the ilium.

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PANCREATIC TISSUE IN THE WALL OF THE STOMACH

E. S. J. KING, M.S., F.R.C.S.
Surgeon to Outpatients, Melbourne Hospital

AND

P. MacCALLUM, M.C., M.A., M.Sc.
Professor of Pathology, University of Melbourne
MELBOURNE, AUSTRALIA

Nodules of tissue indistinguishable microscopically from pancreas have been observed by many investigators and have been discussed at length, deservedly, in numerous papers. Not only is such a phenomenon of considerable interest, but it presents a fundamental pathologic problem. In many of the papers that have appeared, not only have hypotheses which are untenable in the present state of knowledge been proposed, but even patently inaccurate observations have been made. In addition, certain relevant features of considerable import in the determination of the nature of these masses have been overlooked.

HISTORICAL DATA

The earliest record of the occurrence of pancreatic tissue in the stomach which is available to us is that of Zenker, published in 1861. He referred to a previous note by Klob in 1859, and to some observations in lower animals by Leydig (1857).

Wagner (1862) and Gegenbauer (1863) reported other cases, and a few further reports appeared, until at the beginning of this century much interest was manifested in the condition. Thorel (1903) described seven cases of "aberrant pancreatic tissue," in three of which the tissue was in the stomach. In 1904, Warthin collected forty-seven similar cases from the literature, and in thirteen of these the aberrant tissue was in the stomach. He described one other case. Horgan, in 1921, collected thirty-two other cases, in five of which the condition was in the stomach. Beutler gave a good account of the literature.

Since then numerous accounts have appeared, some as special references to the occurrence of pancreatic tissue in the stomach, Delhougne, 1924; Griep, 1926; Hilarowicz, 1927; Münch, 1925; Vandendorp, 1928), and others in which the condition is merely referred to during a discussion on related subjects (Nicholson).

HYPOTHESES

The majority of the hypotheses of the origin of these tissues are closely interrelated.

Zenker suggested that they represent an anomaly occurring in early embryonic life in which an additional diverticulum arose from the duodenum. With growth of the tissues this supernumerary diverticulum became separated from the normal structure. Glinski postulated that one or more of the anlagen of pancreatic tissue failed to coalesce. Either of these hypotheses could explain only pancreatic tissue in the duodenal wall. Since the duodenum has been demarcated from the stomach at the time of budding of the pancreatic tissue, abnormalities of this bud cannot be carried into the contiguous parts of the intestine.

Warthin's view was that lateral budding of the rudimentary pancreatic ducts occurred as they penetrated the wall of the intestine. Since pancreatic tissue has been found in the cardia of the stomach and in Meckel's diverticulum, the budding must have proceeded with peculiar enthusiasm.

Horgan adopted an even more fanciful hypothesis. In describing the development of the pancreatic outgrowths, he said: ". . . branching buds come into contact with the wall of the stomach, intestine or mesentery and may become engrafted thereon." Such a view, apart from inherent improbabilities, does not adequately deal with tissue (*a*) on the anterior wall of the stomach, (*b*) in the submucous coat or, most particularly, (*c*) in Meckel's diverticulum, which lies anterior to the intestine, whereas the pancreatic bud, certainly the part referred to by Horgan, is mainly posterior.

PATHOLOGIC PRINCIPLES

In order to appreciate the difficulties which surround the subject and also to understand the reason for diverse opinions on some pathologic problems, it is necessary to consider the mode of development of pathologic thought.

It is axiomatic that pathology must conform with the fundamental sciences—biology and embryology. When pathology began to make rapid advances about seventy or eighty years ago, embryology was also advancing quickly. The principles laid down by the embryologists were accepted by pathologists and applied to pathologic processes. One such principle was that of the immutability of the germ layers. Another was the idea that the capabilities of cells for growth or further differentiation gradually diminished with differentiation. From this it followed that differentiated adult cells had lost all power of the formation of other tissues, and as a corollary of this, unusual tissue found in an organ must be derived from undifferentiated (or embryonic) cells.

From this principle was evolved Cohnheim's hypothesis of cell rests. When portions of tissue were found in an unusual situation, e. g., pancreatic tissue in the wall of the stomach, it was argued that since the adult cells had lost the potentialities of the original intestinal epithelium to give rise to various types of epithelia, this tissue must have arisen at a time when the cells of the intestine still retained a multipotential character, i. e., during embryonic life, or else certain of such embryonic cells remained latent within the limits of this hypothesis. The hypothesis of a "cell rest" with minor modifications is still strongly entrenched in pathologic thought and writings, in flagrant defiance of the principle that current pathologic opinion should advance with biology and embryology.

Cohnheim's hypothesis depends on embryologic views of eighty years ago. Has this science advanced since then and have any of its fundamental principles been altered? If so, then one must modify one's views in conformity with them. The failure of a great many modern pathologic investigations is caused by the fact that, so far as many investigations are concerned, pathology·has become segregated from biology and to a less extent from embryology, and until rapport is established and a broad outlook adopted true advance must be retarded.

Recent investigations have shown that the potentialities of adult cells for proliferation and change into those of related but different type are not always lost, but are retained in varying degrees in different tissues. There is no doubt that accompanying progressive differentiation during development a certain inflexibility is imposed on cells. This corresponds with the fixation of morphologic attributes in certain parts of even the ovum, e. g., in some Coelenterata.

On the other hand, certain tissues retain, within certain limits, an extraordinary capacity for growth and alteration into tissue of a related type. Modern biologic and pathologic investigation is demonstrating the accuracy of this view. The reformation of synovial membrane (Key) and menisci (A. Gibson), the development of a new lens from the iris after removal of the original lens (Sato), the formation of the alimentary canal of insects from the epithelium (epiblastic in origin) of the foregut (Mansour) and the development of various glands (intestinal and gastric) from the epithelium of the gallbladder (King, 1930) support this suggestion. If this is so, then the raison d'être of Cohnheim's hypothesis disappears.

It is proposed to deal here with the observations made on four pathologic specimens, and to bring forward evidence from them that such tissue is not a "cell rest," does not arise during embryonic life and develops from differentiated tissue usually during postnatal, and most often in adult. life.

REPORT OF CASES

CASE 1.—S. D., a man, aged 37, complained of indigestion of two years' dura-
tion. Repeated roentgen examination revealed spasm of the wall of the stomach
at the proximal end of the pyloric antrum, which was not completely relieved by
the injection of atropine.

At laparotomy a localized nodular thickening, about three-fourths inch (1.87
cm.) in diameter, was found on the anterior surface of the stomach near the greater
curvature, about 2½ inches (6.27 cm.) from the gastroduodenal junction. This
was removed.

Fig. 1 (case 1).—Low power photomicrograph of a section of a nodule of
pancreatic tissue in the wall of the stomach, showing the muscle bundles lying
between the pancreatic lobules; × 24.

Microscopic examination showed that the tissue was composed almost entirely
of pancreatic tissue lying between bands of muscle. Some of the tissue resembled
pancreas, but was not completely differentiated (fig. 1).

CASE 2.—P. N., a man, aged 47, complained of indigestion of two years' dura-
tion. Vomiting had been becoming more severe for the four months before opera-
tion. Roentgen examination revealed an almost complete obstruction of the pylorus.
Resection of the pyloric portion of the stomach (Polya's operation II) was per-
formed.
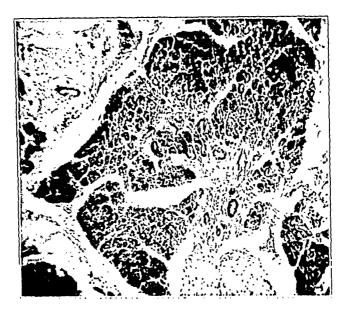
Fig. 2 (case 1).—Photomicrograph, showing the structure of the pancreatic tissue in a nodule in the wall of the stomach; × 100.
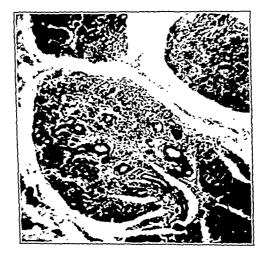
Fig. 3 (case 1).—Photomicrograph of a portion of tissue lying among the "pancreatic" lobules. This is not morphologically typical pancreatic tissue. There are many ducts and an indeterminate (? undifferentiated) type of epithelium; × 100.

Microscopically, the tissue consisted of masses of epithelial cells, mainly of the Brunner type, but some undifferentiated, and a few pancreatic acini. There was no evidence of malignant development.

CASE 3.—S. G., a man, aged 72, died of chronic nephritis and cardiovascular disease. Routine postmortem examination revealed a small thickening on the posterior surface of the stomach near the lesser curvature, two thirds the distance from the cardia to the pylorus. It measured one-fourth inch (0.64 cm.) in diameter.

Microscopically, well developed pancreatic tissue was found in the deep portion of the wall. Between this and the mucosa there was undifferentiated epithelium in the form of tubules lined by columnar epithelium. Some of the tubules were in close relationship with the mucosa, and others were closely connected and appeared to be continuous with the pancreatic tissue. In some places there were a few pancreatic alveoli in the submucous coat.
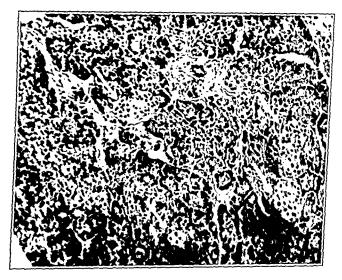
Fig. 4 (case 1).—Portion of pancreatic tissue in the wall of the stomach, showing islets of Langerhans (marked by arrows) ; × 140.

CASE 4.—A. V., a man, aged 53, reported at the hospital with symptoms suggestive of a chronic gastric ulcer. The diagnosis was confirmed by roentgen examination. Wide excision of an ulcer in the lower part of the cardia was performed.

Microscopic examination of the specimen showed remarkable epithelial proliferation in the neighborhood of the ulcer. Mucous glands, Brunner's glands and intestinal epithelium were present, and in a few areas there were groups of pancreatic acini (fig. 10).

COMMENT ON CASES

Three features of these cases are worthy of consideration.

1. *Age.*—All of the patients were relatively old, three being over 45. This fact was noted in many of the reports of examples of "cell rests." This observation alone should give one pause when attempting to explain the condition on a "congenital" basis. There is no reason why cellular

changes should not occur in children if the adequate stimulus were applied. Probably the absence of such phenomena in the young is to be correlated with their relative freedom from many chronic diseases. Hale reported a case of "pancreatic tissue" in the pylorus of an infant suffering from hypertonic stenosis of the pylorus. A brief scrutiny of his illustrations demonstrates that he apparently mistook Brunner's glands for pancreatic acini.

2. *History.*—The majority of patients give a history of symptoms of recent onset referable to the region involved. It is possible, of course, that the "rest" may have lain latent for fifty years and that another
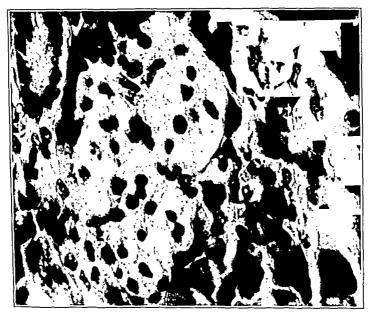
Fig. 5 (case 1).—High power view of an islet similar to those shown in figure 4; × 750.

lesion was superimposed on it, or even that it determined the site of the disease, e. g., ulcer. This is but multiplying hypotheses instead of proving them.

3. *Relationship to Inflammation.*—Evidence of inflammation is present in most cases, and since epithelial proliferation readily occurs in such areas, a close causative relationship of the epithelial structures to this process seems probable. Not only proliferation but metaplasia is frequently observed in association with an area of inflammation; e. g., various kinds of epithelium of the alimentary canal may be found in the chronically inflamed gallbladder (King); "gastric" glands have been found adjacent to a tuberculous ulcer of the colon (Nicholson, *b*), and

intestinal epithelium is a common finding in inflammatory conditions of the stomach.

In case 4 there was strong evidence of the recent development of pancreatic tissue directly from the gastric mucosa. Pancreatic tissue is associated with other epithelia; in the submucous layer it is closely associated with the gastric epithelium, and in some places it is directly continuous with it.

In case 3 there was no evidence of inflammation, but the pancreatic tissue was connected with the surface epithelium by ducts which were lined by cells that did not correspond with any normal adult type. The stimulus that caused its development had disappeared, or at least there was no evidence of its presence.
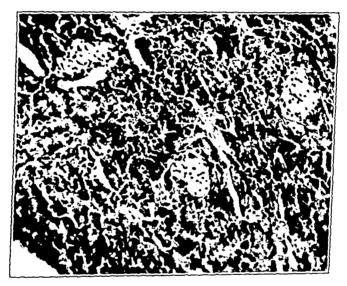
Fig. 6 (case 3).—Portion of pancreatic tissue showing islets; × 140.

MICROSCOPIC FINDINGS

The glands consist of collections of acini grouped in a characteristic manner. Among the acini there usually are groups of cells which morphologically correspond to islets of Langerhans.

The cells of the acini show two characteristic zones: an inner zone containing granules and an outer, nongranular zone, staining with hematoxylin and containing the nucleus. The cells appear to conform in all particulars with those of normal pancreas.

The tissue may appear in the subserous layer, in the muscular layer or in the submucous coat. From a consideration of the literature, Delhougne gave the distribution as in the accompanying table.

The frequency of occurrence of aberrant pancreatic tissue corresponds closely to the distribution of peptic ulcer of the stomach. Most

observers agree that ulceration of the stomach is a postnatal develop-
ment and due to definite pathologic phenomena. This similarity of
distribution forms another link in the chain of evidence for a postnatal
origin of the pancreatic tissue, more especially since the distribution
is not readily explicable embryologically.

In all of these situations the glandular tissue is intimately mingled
with the tissue of the part; e. g., when glandular tissue is present in
the muscular coat, the groups of acini lie among the muscle bundles.
This, in itself, seems to put considerable difficulty in the way of accept-
ing the hypothesis of a "rest." If a "rest" of pancreatic tissue occurred
in the wall of the stomach, one would expect that in its growth it would
displace contiguous material, and that it would resemble the normal
gland, which does not contain bands of muscle between the groups of
acini.

Delhougne's Distribution of Tissues

Cases	Location	Percentage	
15	Submucous	45.4	
5	Intramural	15.1	
5	Subserous	15.1	33 cases
8	More than one layer	24.2	
14	Pylorus	58.3	
3	Greater curvature	12.5	
5	Lesser curvature	20.8	24 cases
2	Cardia	8.3	

The close association of the pancreatic tissue with muscle bundles is
similar to the association of glands which have grown down from the
epithelium in cases in which the epithelium is stimulated, e. g., in the
neighborhood of a gastric ulcer.

Islets of Langerhans are frequently found throughout the tissue.
Characteristically, they are present in the masses of pancreatic alveoli,
but in other parts they may be found alone or in association with ducts
(fig. 8). In some cases they have been found arising apparently from
acini, either as an outgrowth from the acinar tissue (fig. 9), or by a
change in the acini themselves (fig. 5).

Atypical cells and acini form groups among the typical pancreatic
tissue. Some of them form complete groups not connected with the
contiguous pancreas, but in other cases they merge into the pancreatic
acini so that a portion of a mass of acini is pancreas and the remainder
is atypical in character.

These associated acini are less deeply staining than those of the true
pancreatic type; they are slightly larger, and many of them have a small
central space. The cells are of about the same size as the pancreatic
cells; the protoplasm has few or no deeply staining granules, and the
nuclei are more vesicular and have less deeply staining chromatin.

Ducts lined by cuboidal epithelium and with a well formed muscular coat are found among all the cell groups, whether typical or atypical in appearance. In many cases the ducts may be found in deeply situated masses, passing up through the wall of the stomach to the mucous surface. Here again a serious difficulty is opposed to the acceptance
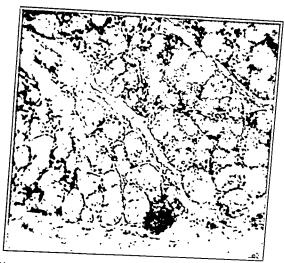
Fig. 7 (case 2).—Photomicrograph of a portion of the wall of the stomach, showing Brunner's glands and one acinus of the pancreatic type. There were other typical pancreatic lobules in the vicinity; × 165.
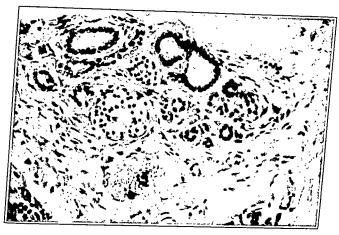
Fig. 8 (case 3).—Photomicrograph of portion of a section of the nodule. There are well formed islets among the ducts; × 140.

of some phases of the hypothesis of a "rest." Misplaced tissue should, by the course of its ducts, show some indication of its origin, and the ducts should run along the wall toward the duodenum. In fact, they are continuous with the mucosa that lies above, irrespective of whether it is stomach, intestine or Meckel's diverticulum. The biologic meaning

Fig. 9 (case 3).—Another portion of the nodule, showing a continuity between alveoli and islet tissue; × 140.

Fig. 10 (case 4).—Photomicrograph of a portion of the mucosa of the stomach, showing epithelial proliferation and metaplasia, with the formation of pancreatic lobules; × 38.

of this peculiarity according to the hypothesis of a "rest" is at least nebulous.

The pancreatic tissue may be independent of other epithelial structures (case 1, fig. 1); it may be associated with atypical (probably undifferentiated) tissue (case 3), or it may be associated with other glandular elements (case 4, fig. 10). This pancreatic tissue is sometimes related to the other glands by way of undifferentiated tissue, as in the case reported by Woolsay and Millzner.

Our observations confirm this relationship. It is one which strongly suggests that a glandular tissue (e. g., Brunner's glands) has undergone dedifferentiation, and that the cells have been differentiated to form the pancreatic tissue. In some parts of the body, e. g., in the gallbladder, it is possible to find glands of an unusual form ("aberrant") in close association with the normal cells of the part and almost certainly arising from them without any intermediate stage. Presumably in such cases the intermediate step has passed, and one has to postulate such a stage from the morphologic appearances.

In the stomach a similar appearance may be encountered. At the edge of a mass of Brunner's glands a single acinus resembling a pancreatic gland may be found (fig. 7). Apart from its morphology, its nature is suggested by the presence of pancreatic tissue in the neighborhood.

SUMMARY

1. From a study of four cases of pancreatic tissue in the wall of the stomach and a review of the literature it is concluded that pancreatic tissue arises from the epithelium of the stomach under the action of abnormal stimuli and does not arise as a "cell rest" from the displacement of a pancreatic anlage during embryonic life.

2. The reasons for this conclusion are:

(A) Such tissue is connected directly or indirectly with the overlying epithelium.

(B) Continuity of such tissue with the gastric epithelium can undoubtedly be directly traced in some cases.

(C) The tissue is found mainly (if not entirely) in adults and mainly in old people, thus suggesting a postnatal development.

(D) The distribution of pancreatic tissue in the stomach corresponds to that of obviously acquired lesions, such as a gastric ulcer.

(E) No morphologic connection is found between these masses and the anatomic pancreas.

(F) The pancreatic tissue does not occur as a discrete mass of tissue occupying a portion of the wall, but is intimately mingled with the structures of the wall of the stomach.

3. Reasons are given for considering that the various embryologic "explanations" which have been proposed are inadequate and do not take cognizance of known embryologic laws.

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EXPERIMENTAL OCCLUSION OF THE PULMONARY ARTERY

AN ANATOMIC STUDY

CYRUS F. HORINE, M.D.

AND

C. GARDNER WARNER, M.D.

BALTIMORE

The increasingly frequent occurrence of postoperative pulmonary embolism with its dreaded and often fatal results is probably responsible for the stimulation of interest in the subject of experimental occlusion of the pulmonary artery. Numerous investigators have approached the subject from as many different angles. The literature has been reviewed by Schlaepfer.[1] Experiments performed by this investigator on rabbits and dogs showed that ligations of a branch of the pulmonary artery did not result in marked fibrosis as had been shown by Bruns,[2] Sauerbruch,[3] Kawamura,[4] Smirnoff[5] and others. Schlaepfer did produce extensive fibrosis, however, by cutting the phrenic nerve when ligating the corresponding pulmonary artery. Schlaepfer's experiments on dogs were carried out, however, through a transpleural approach. In the experiments on rabbits the branch of the pulmonary artery was ligated through a pericardotomy opening without causing pneumothorax.

In any mechanism so complicated as that of the so-called cardio-respiratory apparatus, in which there is so much interdependence, the changes in pressure caused by operative pneumothorax might materially alter the subsequent anatomic findings.

This article will deal chiefly with the anatomic findings in the dog's lung subsequent to ligation of the right pulmonary artery or one of its branches. A method of exposure of the pulmonary vessels devised by

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From the Departments of Surgery and Pathology of the University of Maryland School of Medicine.

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one of us (C. F. H.[6]) was used in these experiments. This method interferes less with the normal physiologic activity of the cardio-respiratory mechanism, both during the experiments and after recovery, than either the transpleural or the transpericardial approach.

EXPERIMENTAL METHOD

Young normal dogs, preferably of the terrier, beagle or bull types, were used in these experiments. The broad chest and rather short neck which characterize dogs of these types favored exposure of the mediastinal vessels. The dog was anesthetized with ether, and under aseptic technic an opening was made in the mediastinum through a longitudinal incision over the trachea. From this incision the dissection was carried down through the thorax between the pleural cavities on either side, to the base of the heart. A small incision was made in the connective tissue which covers the pulmonary artery outside of the pericardium. A ligature was passed around the right branch or its secondary division with an aneurysm needle. This ligature was tied by using long clamps. Two ligatures may be applied, between which the artery may be severed. The animals were killed after variable periods ranging from one week to fifteen months, although the anatomic changes as recorded in the x-ray pictures were followed in several animals beginning a few hours after ligation of the pulmonary artery. In each instance the animals were killed by deep ether anesthesia. The trachea was clamped before the animal ceased to breathe. An injection of a diluted solution of formaldehyde, U. S. P. (1:10), into the trachea was made to fix the lungs before collapse. After a small amount of formaldehyde was introduced, another needle was placed in the trachea to allow air to escape. The formaldehyde was injected slowly by gravitation, and the injection was completed when the solution began to flow from the second needle. The chest was opened after from fifteen to twenty minutes. The common carotids, thoracic aorta and venae cavae, as well as the trachea, were ligated before the thoracic contents were removed. The heart and lungs were then placed in formaldehyde for twenty-four hours.

EXPERIMENTAL RESULTS

In none of the dogs was there any deformity of the chest, but when the thorax was opened in 2 dogs in which the entire right pulmonary artery had been ligated, the heart and mediastinum were found displaced toward the side of the ligation. In all the dogs the operative wound in the mediastinum healed without infection, and at autopsy only a few adhesions in the mediastinum around the pulmonary vessels were encountered. In several of the dogs metal skin clips were used to occlude the branches of the pulmonary artery; in others, either single or double silk ligatures were used. In the two dogs in which the pulmonary branch had been ligated for fifteen months, the lumen of the occluded branch was obliterated and only a fiber-like cord remained. In those in which the ligation was of shorter duration, the lumen of the ligated vessel contained organized thrombi. The lung or lobe supplied by the

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ligated vessel was always smaller than the intact one. The pleural sacs
of the dogs showed no adhesions or excess fluid, although the visceral
pleura in some showed definite thickening. There was always a ten-
dency toward "wrinkling" of the visceral pleura over the lobes in
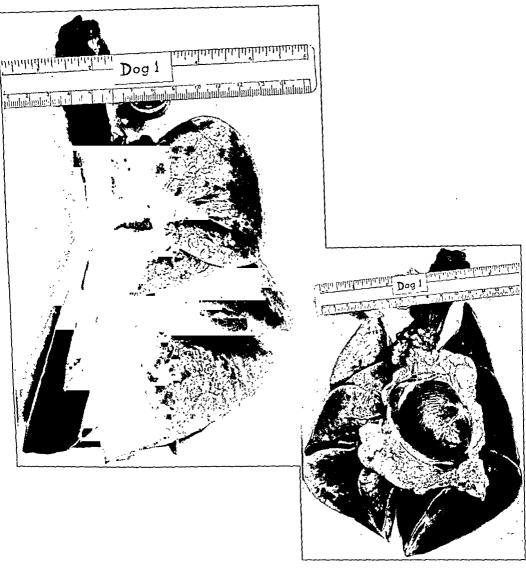
Fig. 1 (dog 1).—Lateral view of the upper lobe of the right lung, taken fifteen
months after ligation of the pulmonary artery which supplied the lobe. Note the
presence of small pleural vessels in the upper lobe. The lower lobe, supplied by
the unligated artery, does not have macroscopic vessels. The inset shows the
anterior view of the heart and lungs of the same dog.

which the branch of the pulmonary artery had been occluded. Areas of emphysema could be demonstrated in both lungs, especially in the lobe supplied by the nonligated branch. Several of the lungs supplied by ligated branches showed gross evidence of old hemorrhage into air sacs, with some organization. These areas were unlike infarcts in that there was no dulling of the pleura or collection of fibrin on its surface. Practically all of the dogs had enlargement of the right ventricle, and
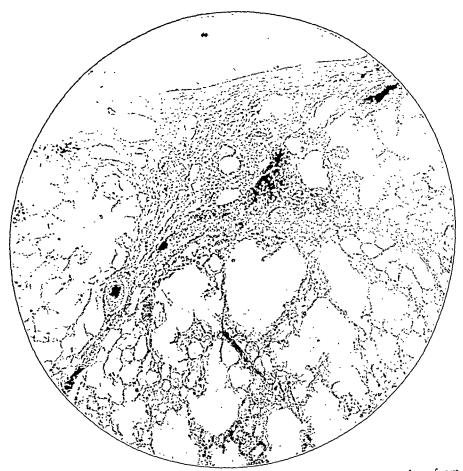
Fig. 2 (dog 1).—Photomicrograph of an unstained frozen section taken from the upper lobe of the right lung. Note the increase in perivascular connective tissue; × 80.

in some cases a deep sulcus could be seen between the apexes of the ventricles. There was little evidence of an increase in the thickness of the visceral pleura except in the dogs in which a branch of the pulmonary artery had been ligated fifteen months previously. The increase in connective tissue in these two cases was for the most part subpleural, although there was some increase in the amount of fibrous tissue in the interstitial spaces under the pleura, as shown in figures 1 and 2. Particular attention is called to the prominence of subpleural vessels over

the lobes supplied by the ligated artery. These are either new vessels or preexisting bronchial vessels the caliber of which has increased since ligation.[7] Some of these vessels measured as much as 1 mm. in diameter. The fact that such prominent subpleural vessels were not found on the side of the unligated artery seems to indicate that these vessels are concerned in the compensatory mechanism following pulmonary occlusion. They may possibly represent a collateral anastomosis between bronchial and pulmonary vascular systems. That many of these subpleural vessels
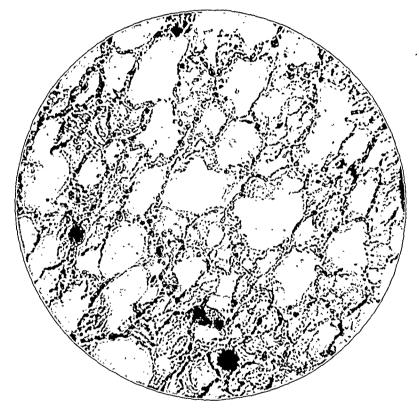
Fig. 3 (dog 1).—Photomicrograph of a thick, frozen section of the upper lobe of the right lung fifteen months after ligation of the pulmonary artery that supplied the lobe. Note the uniformity in size of the alveoli and of the interalveolar capillaries; $\times$ 135.

are derived from the bronchial vascular system was shown by us by the injection of pigment.[7] One would think that adhesions would develop between the visceral and the parietal pleura as a means of establishing a collateral circulation with vessels of the wall of the chest, but this was not the case in any of the eight experiments. Definite

7. Horine, C. F., and Warner, C. G.: Distribution of the Pulmonary Circulation in the Dog, J. Thoracic Surg. 2:80, 1932.

enlargement of the bronchial arteries and of their branches anastomosing with the esophageal artery could be seen without the injection of pigment four weeks after ligation of the right pulmonary artery.

Microscopic examination of the intact lung showed interesting changes. Some of the changes could be seen as early as two hours after ligation of a branch of the pulmonary artery. These findings, after ligations of such short duration, were observed by us in connection with experiments on the pathologic physiology following occlusion. The
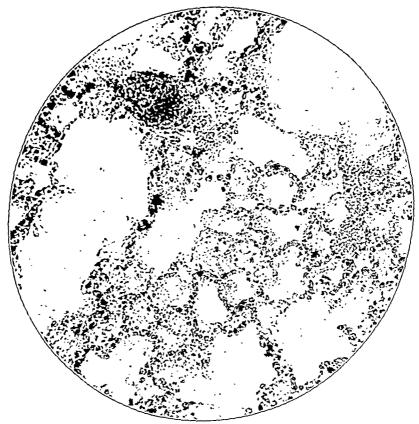
Fig. 4 (dog 1).—Photomicrograph of an unstained, thick, frozen section of the upper lobe of the left lung. The pulmonary artery supplying this lobe was not ligated. Note the areas of emphysema and the increase in interalveolar capillaries; $\times$ 135.

pathologic changes consisted chiefly of enlargement of the alveolar sacs with rupture and fragmentation of the walls. The interalveolar capillaries were enlarged and dilated. These changes were most marked about four weeks after ligation; in fact, there seemed to be a basket-like network of capillaries in each alveolar wall, as shown in figure 5. The increase in size of the individual alveolus, together with the compensatory emphysematous condition of the whole lobe or lobes of the lung on the side of the nonligated artery, would account for the increase

in size and probably contribute toward the displacement of the heart and mediastinum toward the side of the ligated artery. An immediate decrease in the volume of the lung, or at least a decrease in the volume of the blood, is expected after occlusion of its corresponding artery. With the decrease in the volume of the blood there should be an increase in the negative intrapleural pressure, because as the total volume of the lung on the side of the ligated artery is decreased the size of the potential space on that side should be increased. If a simultaneous compensatory
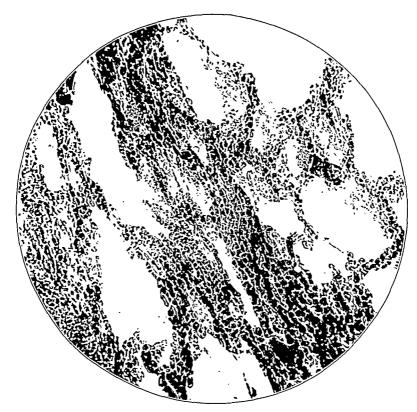
Fig. 5 (dog 4).—Photomicrograph of the lobe of the right lung between three and four weeks after ligation of the corresponding pulmonary artery. Note the area of compression of the alveoli and the surrounding areas of emphysema. Stained with hematoxylin and eosin; × 135.

increase in total volume occurs in the lung on the side of the nonligated artery, a displacement of the structure lying between the two lungs to the affected side should be expected. Figure 7 shows a marked displacement of the apex of the heart to the right. This occurred within ninety-six hours after ligation of the right pulmonary artery. These changes in the volume and pressure could also account for the emphysema.

A microscopic picture of a lung in which a branch of the pulmonary artery had been ligated showed anatomic changes which are difficult to explain. The findings early after ligation consisted of areas of emphysema, as well as of collapse or atelectasis, areas which appeared to show compression of a number of alveoli and their corresponding interalveolar capillaries. Surrounding these areas of compression were found emphysematous sacs with hemorrhage into many alveoli. In some sections, especially those near the periphery of the lung, solid
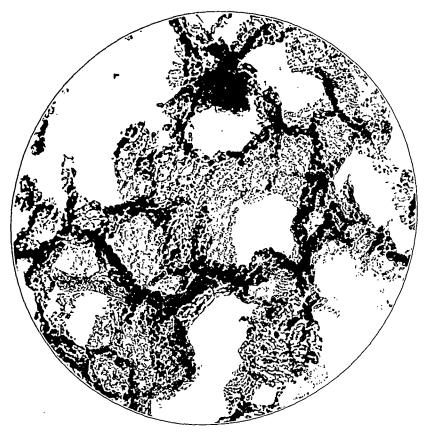
Fig. 6 (dog 4).—Photomicrograph of a thick, frozen section of the lobe of the left lung the pulmonary artery to which was not ligated, taken between three and four weeks after ligation of the right pulmonary artery. Note the areas of emphysema and the more numerous interalveolar capillaries. Stained with hematoxylin and eosin; × 135.

masses of hemorrhage were noted beneath an intact pleura, without exudation on, or thickening of, that membrane. In not a single instance were adhesions found between the opposing pleural surfaces where this type of hemorrhage existed, even in specimens which showed some evidence of organization of the hemorrhage. Deeper in the pulmonary tissue, that is more centrally, the hemorrhage was less evident.

Only in the two dogs in which a branch of the pulmonary artery had been ligated fifteen months previously was there an increase in the interstitial connective tissue, and in these it was very slight and confined chiefly to subpleural thickening. It was most evident around the visceral pleural vessels previously mentioned. In these two dogs, the general histologic appearance of the pulmonary tissue in the lobes on the side on which the pulmonary artery had been ligated was that of air sacs of uniform size, but somewhat smaller than normal. There was also
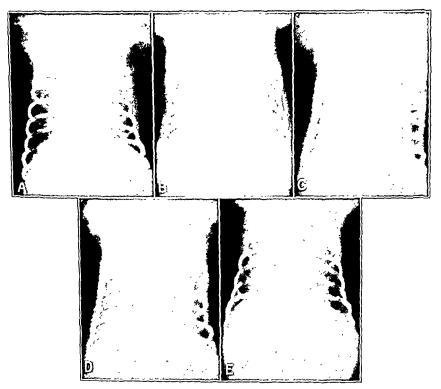
Fig. 7 (dog 7).—Series of roentgenograms showing the displacement of the heart that follows ligation of the pulmonary artery. The right pulmonary artery had been ligated. No attempt was made to bring out the details of the lung. Several of the plates suggest the presence of pneumothorax. The shadows which suggest pulmonary tissue have been cast by the redundant mammary glands of the female dog used in this experiment. It is difficult to obtain accurate plates when the dog is used, but there is very little rotation, if any, in these plates. Note the gradual displacement of the heart and mediastinum toward the right side, or the side of the ligated artery. *A* was taken immediately before ligation; *B*, half an hour afterward; *C*, twenty-four hours afterward; *D*, seventy-two hours afterward; and *E*, ninety-six hours after ligation.

uniformity in the size and the number of capillaries. The basket-like capillary plexus in the alveoli which is present in the normal dog's lung to a modified degree was entirely absent in these two dogs.

Observations on Dogs Studied

Dog	Date and Operation	Course and Symptoms	Roentgenograms Taken	Date of Autopsy	Duration of Experiment	Gross Anatomic Changes	Microscopic Anatomic Changes
1. Black and white terrier	March 18, 1930, mediastinotomy; ligation of right superior pulmonary artery	Wound healed per primam in 10 days; entire course without respiratory or cardiac symptoms; dog gained weight	March 25, April 1 and 8 and July 3, 1930; Feb. 6, 1931	June 10, 1931	15 months	Ligature intact; pulmonary vessel to upper lobe cordlike; heart hypertrophied and dilated, especially on the right side, with a sulcus between the ventricles at the apex; over "ligated lobe"; no free fluid; "ligated lobe" small and shrunken, with the visceral pleura showing a tendency toward wrinkling	Increased subpleural connective tissue, especially in interstitial spaces around vessels; hypertrophy of preexisting bronchial vessels in lung; compensatory bronchial vessels in lung; increased number of interalveolar capillaries; scattered areas of emphysema and atelectasis of "ligated" lobe; obliteration of groups of sacs from organization of hemorrhage; decreased number of interalveolar capillaries in "ligated" lobe
2. Mixed fox terrier and beagle	April 10, 1930, mediastinotomy; ligation of right inferior pulmonary artery	Wound healed in 7 days; recovery without symptoms	April 17 and 25, 1930, and Feb. 6, 1931	July 10, 1931	15 months	Ligature intact; pulmonary vessel to lower lobe obliterated; heart hypertrophied; right lower lobe somewhat shrunken, with gross areas of hemorrhage under the pleura; no inflammatory reaction on the overlying pleura; some compensatory emphysema of the opposite lung	The same general findings as in dog 1
3. Mixed bull and beagle	May 19, 1931, mediastinotomy; ligation of right pulmonary artery	Recovery complete and wound healed in 7 days; no cardiorespiratory symptoms	....	June 2, 1931	2 weeks	Ligature intact; right pulmonary artery showed a thrombus in lumen; right side of heart dilated; right lung smaller; compensatory emphysema on left	No increase in connective tissue in interstitial tissue; scattered areas of emphysema and atelectasis, with hemorrhage into air sacs at periphery of lung without pleural reaction
4. Tan mongrel	May 18, 1931, mediastinotomy; ligation of right pulmonary artery	Recovery complete; no symptoms throughout experimental period	....	June 8, 1931	3 weeks	Ligature intact; right pulmonary artery grossly occluded; ligated lung small	No increase in connective tissue in interstitial tissue; scattered areas of emphysema, atelectasis and hemorrhage of "ligated" lung; compensatory emphysema of intact lung
5. Black mongrel	Jun. 11, 1931, mediastinotomy; ligation of right pulmonary artery	Recovery uneventful and without cardiac or respiratory symptoms	5 cc. of iodized oil 10 minutes after ligation; Jan. 12 and 13, 1931	Jan. 18, 1932	1 week	Ligature intact; right pulmonary artery occluded; patchy atelectasis	No increase in connective tissue in subpleural tissue; many areas of collapse or interstitial tissue; many areas of collapse
6. Beagle	Jan. 18, 1932, ligation of right pulmonary artery	Shortness of breath throughout course	Jan. 25, 1932; enlarged heart	Feb. 1, 1932	2 weeks	Ligature on right pulmonary artery intact; heart enlarged and dilated, with sulcus between ventricles; no adhesions; no free fluid in cavities of chest	No increase in interstitial connective tissue; scattered areas of emphysema and hemorrhage in "ligated" lung without pleural reaction
7. Black and white mongrel	Jan. 19, 1932, mediastinotomy; ligation of right pulmonary artery	Recovery without symptoms; found dead 2 weeks after operation	1/2 hour, 24 hours, 72 hours and 96 hours after ligation	Found dead Feb. 2, 1932	2 weeks	Ligature intact; no inflammation in mediastinum; heart enlarged and displaced to right; right lung small; no gross explanation as to cause of death found	No increase in interstitial connective tissue; numerous areas of atelectasis with hemorrhage in air sac as in "ligated" lung; "intact"
8. White and tan mongrel	Jan. 27, 1932, mediastinotomy; ligation of right pulmonary artery	Recovery uneventful	Jan. 28 and 29, 1932	Feb. 14, 1932	18 days	Ligature intact; "ligated lung", small, with tendency toward "wrinkling" of visceral pleura; heart enlarged and displaced toward affected side	Pulmonary artery occluded by an organizing thrombus; no increase in subpleural or interstitial connective tissue; scattered areas of emphysema and atelectasis, together with hemorrhage in air sac as noted in "ligated" lung

CONCLUSIONS

1. Scattered areas of emphysema, atelectasis and hemorrhage into the air sacs are produced in the lung by ligating a branch of the pulmonary artery.

2. If the ligation of a branch of the pulmonary artery is performed extrapleurally without pneumothorax, it does not produce a deformity of the chest with marked fibrosis and contraction in fifteen months.

3. Ligation of a branch of the pulmonary artery results in new formation of vessels in the visceral pleura or in an increase in the caliber of preexisting ones.

4. Displacement of the heart and mediastinum to the side of the ligated artery may be seen with the x-rays as early as forty-eight hours after occlusion of the artery.

EXPERIMENTAL OCCLUSION OF THE PULMONARY ARTERY

PATHOLOGIC PHYSIOLOGY

CYRUS F. HORINE, M.D.

AND

C. GARDNER WARNER, M.D.

BALTIMORE

Welch,[1] Plumier,[2] Tigerstedt,[3] Underhill[4] and others have stated that ligation of the pulmonary artery of one lung causes very little or no change in the systemic blood pressure. Haggart and Walker[5] found no significant variation in the general circulation of animals until from 52 to 66 per cent of the pulmonary circulation had been occluded. Tigerstedt[3] showed that there was a slight decrease in the volume output of the left ventricle per minute after one branch of the pulmonary artery had been ligated. Lichtheim[6] found no significant variation of the general circulation after occluding 75 per cent of the pulmonary circulation. Mann,[7] producing pulmonary embolism by the introduction of clots into the venous system (the femoral vein), noted a slight drop in the systemic pressure, which he believed to be due to the passage of the embolus through the valves of the heart. Underhill[4] stated that ligation of the left pulmonary artery in cats (with the chest open and under positive pressure anesthesia) caused an increase in pulmonary arterial pressure from 25 to 60 per cent. He found no effect on the carotid blood pressure, the pulse rate, the output of the heart or its state of dilatation. Haggart and Walker[5] measured the blood pressure in the femoral artery after occluding the pulmonary artery. They clamped the left pulmonary artery and the main pulmonary artery with a special

1. Welch, W. H.: Zur Pathologie des Lungenödems, Virchows Arch. f. path. Anat. **72**:375, 1878.

2. Plumier, L.: La circulation pulmonaire, Arch. internat. de physiol. **1**:176, 1904.

3. Tigerstedt, R.: Ueber den Lungenkreislauf, Skandinav. Arch. f. Physiol. **14**:259, 1903.

4. Underhill, S. W. F.: An Investigation into the Circulation Through the Lung, Brit. M. J. **2**:779, 1921.

5. Haggart, G. E., and Walker, A. M.: The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, Arch. Surg. **6**:764 (May) 1923.

6. Lichtheim, L.: Die Störungen des Lungenkreislaufes und ihr Einfluss auf den Blutdruck, Inaug. Dissert., Breslau, 1876.

7. Mann, F. C.: Pulmonary Embolism: An Experimental Study, J. Exper. Med. **26**:387, 1917.

graduated clamp which was applied through an opening in the wall of the chest. They concluded that with this method it was possible, in the normally breathing dog, to produce partial or complete block of the pulmonary artery, the condition as here brought about being analogous to pulmonary embolism in man. Clamping of the left branch of the pulmonary artery caused an immediate rise in the pulmonary pressure, the increase averaging about 30 per cent. This procedure caused no significant change in the general systemic pressure, or any variation in the size, rate or output of the heart. Ventilation as measured by a spirometer was, however, increased approximately 25 per cent, a moderate hyperpnea resulting. Following total occlusion of the pulmonary artery an immediate reaction occurred; the heart dilated quickly to a marked degree, and the volume output per minute became materially less. The pulmonary pressure rose sharply from 121 to 267 per cent, and then gradually fell to zero. The systemic pressure began to fall immediately and did not recover, while respirations became irregular and shortly thereafter ceased altogether.

Complete obstruction of the main pulmonary artery causes immediate death, and fatalities also occur following unilateral pulmonary embolism, although therapeutic ligation of a main branch of the pulmonary artery in the human being has been followed by recovery (Sauerbruch,[8] Meyer[9] and others). Ligation of a main branch of the pulmonary artery in the dog is fatal only in exceptional cases. The present study was undertaken with the hope that some light might be thrown on the question of the compensatory mechanism following partial pulmonary occlusion.

EXPERIMENTAL METHODS

Twenty-three dogs were used in these experiments. In all instances, the studies were carried out without pneumothorax by a method of mediastinotomy devised by one of us (C. F. H.).[10] An incision was made over the trachea and the dissection continued through the mediastinum to the pulmonary artery between the two pleural spaces.

The artery was occluded either with a clamp or with an untied ligature. The latter method was preferred, since it was less damaging to the wall of the vessel. By the use of an aneurysm needle a ligature was passed around the artery, and occlusion was produced by traction.

RESULTS

Contrary to the opinion of others, it was found that the occlusion of one half of the pulmonary artery, i. e., one main branch, will cause a decrease in the systemic pressure of from 10 to 30 mm. of mercury.

8. Sauerbruch, F.: Die Bronchiektasien, 3me Congrès Soc. internat. de chir., Bruxelles, 1911.

9. Meyer, W.: Surgery of the Pulmonary Artery, Ann. Surg. **32**:189, 1913.
10. Horine, C. F.: Mediastinotomy for Experiments on the Heart and Lungs in the Dog, J. Thoracic Surg. **2**:77, 1932.

This drop usually occurs within four seconds and is followed by a compensatory rise which is carried above the normal pressure line. The compensatory rise in pressure requires from ten to thirty seconds; it varies in the individual animal. Following the rise there is a recession to the normal base line. Thus, an S-shaped curve is produced. This curve is typical of the changes in pressure in the systemic circuit following occlusion of a branch of the pulmonary artery. If the occlusion is released when the carotid pressure returns to the normal base line, another positive curve appears; this is of short duration.

The original decrease in carotid pressure is no doubt due to a decrease in the output of the left ventricle, since, for a time at least, the amount of blood returned to the heart through the pulmonary veins must be reduced. The following questions then arise: What produces the compensatory rise to and above the normal base line, and if the mechanism by which this is produced should be absent or impaired, would the animal not succumb? Is the duration of the systole increased to help maintain a normal pressure? Do the interalveolar capillaries of the unligated lung dilate sufficiently to allow an increase in volume to the left side of the heart? Is there a reflex stimulation of the vasoconstrictors in order to increase peripheral resistance and thereby maintain normal systemic pressure?

The compensatory rise in pressure may be due to one or several combined mechanisms. The same type of curve is obtained if the pulmonary artery is occluded after both vagi have been severed or the animal has been atropinized. In several animals the vagi were cut and the spinal cord severed at the seventh cervical segment. According to Keng,[11] the phrenic nerve in the dog arises from the fifth and sixth cervical segments.

An immediate decrease in pressure occurs after section of the cord. After the pressure has established a normal base line the right pulmonary artery is occluded. An immediate decrease in the systemic pressure develops without the usual compensatory rise. If the artery remains obstructed, the dog will die. A dog the vagus and cord of which were sectioned was given epinephrine to obtain an epinephrine curve, and after the circulation had been reestablished following the injection of epinephrine another dose was given. At the beginning of the epinephrine curve, the right pulmonary artery was occluded. There followed an immediate decrease in the carotid pressure, with a subsequent compensatory rise. The occlusion of the pulmonary artery was then released, and a greater rise occurred. On the fall of the epinephrine curve, the right pulmonary artery was occluded again. An abrupt fall in systemic pressure was noted, but the usual compensatory rise in

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11. Keng, L. B.: On the Nervous Supply of the Dog's Heart, J. Physiol. **14:** 467, 1893.

pressure did not follow. The pressure continued to decrease until the occlusion had been released. In the dog, the vagus and cord of which are sectioned, plus occlusion of the right pulmonary artery at the time of the rise in the epinephrine curve, the compensatory rise after occlusion will be in proportion to the amount of epinephrine given.

ILLUSTRATIONS

The illustrations are photographs of kymographic tracings made in experiments 2, 10, 5, 13, 7 and 4. The top line in each illustration is the respiratory record, the middle line is the carotid blood pressure curve (except in experiment 13, the pressure was recorded from the femoral artery), and the lower line represents time.
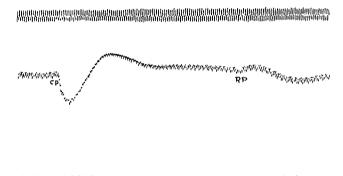
Fig. 1 (experiment 10).—The typical S-shaped curve of the carotid blood pressure record produced by occlusion of the right pulmonary artery. *CP* marks the point of occlusion of the pulmonary artery. The occlusion was released at *RP*. The markings are timed to two seconds. In addition to the S-shaped curve, note the momentary decrease in amplitude of respirations at *CP* and the increase in pressure at *RP*. The blood pressure was measured in millimeters. A decrease of 26 mm. occurred at *CP*.
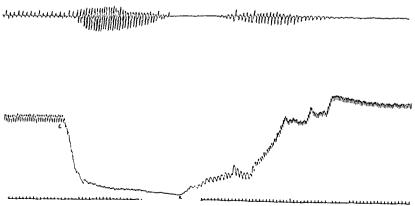
Fig. 2 (experiment 2).—Between 75 and 100 per cent of the pulmonary artery was occluded at *C* and released at *R*. A decrease of 77 mm. occurred in seven seconds. Note the increase in rate and amplitude of respiration during the decrease in blood pressure.

Fig. 3 (experiment 5).—Epinephrine curve. One minim (0.06 cc.) of epinephrine was injected intravenously at *A*. Time in seconds.
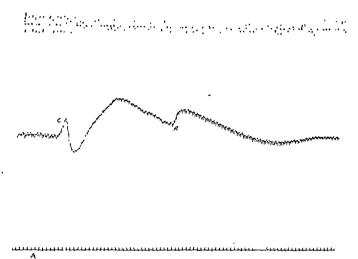
Fig. 4 (experiment 5).—One minim (0.06 cc.) of epinephrine was injected at *A*. On the rise of pressure, the right pulmonary artery was occluded at *C* and released at *R*. Note the exaggerated S-shaped curve with a quicker return to the normal base line after occlusion at *C*. Time in seconds.
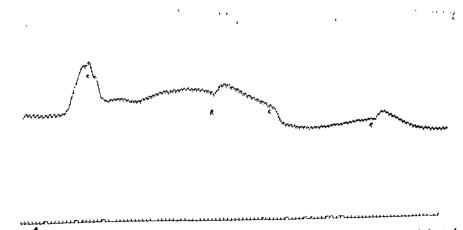
Fig. 5 (experiment 5).—One minim (0.06 cc.) of epinephrine was injected intravenously at *A*. The right pulmonary artery was occluded at the top of the epinephrine curve at *C* and released at *R*. It was clamped again on the fall of the epinephrine curve at *C* and released at *R*. Time in seconds.
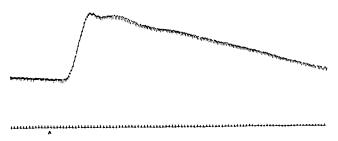
Fig. 6 (experiment 5).—The spinal cord was severed at the seventh cervical segment and 1 minim (0.06 cc.) of epinephrine was injected intravenously at *A*. This figure illustrates the epinephrine curve in a dog the spinal cord of which had been sectioned. Time in seconds.
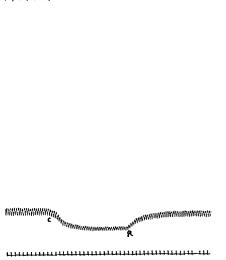
Fig. 7 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment, and the right pulmonary artery was occluded at *C* and released at *R*. Time in seconds.
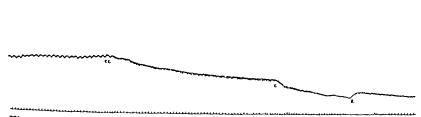
Fig. 8 (experiment 7).—The spinal cord was sectioned at the foramen magnum, and artificial respiration was given with a Masters pump. No record was made of the respirations. The cord was cut at *CC*, and the right pulmonary artery was occluded at *C* and released at *R*. Time in seconds.

Fig. 9 (experiment 4).—The vagi and spinal cord were cut (seventh cervical segment). The right pulmonary artery was occluded at C and released at R. Time in seconds.
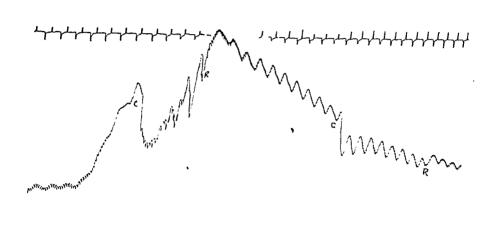
Fig. 10 (experiment 10).—The cord was sectioned at the seventh cervical segment, and the vagi were also cut. One minim (0.06 cc.) of epinephrine was given at A. The right pulmonary artery was occluded at C and released at R.
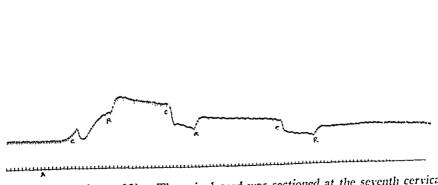
Fig. 11 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment. One minim (0.06 cc.) of epinephrine was given intravenously at A, and the right pulmonary artery was occluded at C and released at R.
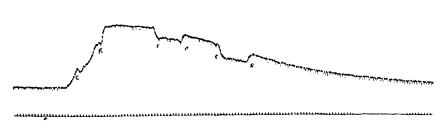
Fig. 12 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment. Two minims (0.12 cc.) of epinephrine was given at *A*. The right pulmonary artery was occluded at *C* and released at *R*. In comparison with figure 11, the decrease in pressure at *C* was not as great, and the recovery between *C* and *R* was quicker on the rise of the epinephrine curve.
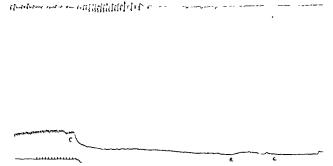
Fig. 13 (experiment 13).—The spinal cord was sectioned at the seventh cervical segment. The right pulmonary artery was occluded at *C* and released at *R*. Note the decrease in pressure with no tendency to recover.

COMMENT

It must be admitted that this problem cannot be definitely and conclusively proved beyond a question of doubt until it has been shown whether or not there is an increase or a decrease in the volume of blood passing through the unobstructed lung per minute after one branch of the pulmonary artery has been occluded in the closed chest. What happens to the capillary bed in the unobstructed lung is not definitely known, although it has been shown (Horine and Warner [12]) that there is a marked dilatation of the capillaries in the unligated lung as early as two hours after occlusion of a branch of the pulmonary artery. But this compensatory rise occurs within thirty seconds at most, and there are no anatomic data to indicate what changes may occur within so short a time.

Assuming that the initial decrease in the carotid pressure in the normal dog after occlusion of the right pulmonary artery is due to a

12. Horine, C. F., and Warner, C. G.: Experimental Occlusion of the Pulmonary Artery: An Anatomic Study, Arch. Surg., this issue, p. 139.

decrease in the output of the left ventricle, the compensatory rise in pressure is built up by an increase in the volume of blood passing through the remaining unobstructed lung per minute and then given to the left ventricle, by an increase in the peripheral resistance in the systemic circuit, by the ability of the muscle of the heart to increase the duration of systole to maintain or to increase that pressure, or by a combination of the aforementioned mechanisms.

A review of the literature shows that no experimental work has been done to determine the immediate volume of blood flowing through the unobstructed lung during the compensatory rise in pressure. Our

Observations on Dogs

Dog	Time for Maximum Decrease in Blood Pressure, Seconds	Amount of Maximum Decrease in Blood Pressure, Mm.	Time for Recovery of Blood Pressure to Normal, Seconds	Blood Pressure Curves	Respiration
1	4	12	14	Decrease in amplitude	Temporary slight decrease in amplitude
2	7	77	22	Decrease in rate and amplitude	Increase in rate and amplitude
3	8	11	20	Decrease in amplitude	No change
4	5	9	27	Decrease in amplitude	Slight temporary decrease in amplitude
5	3	19	13	Decrease in amplitude	Increase in rate and amplitude
6	3	28	30	Decrease in amplitude	Slight temporary decrease in amplitude
7	4	11	13	Decrease in amplitude	No change
8	4	18	13	Decrease in amplitude	Slight temporary decrease in amplitude
9	4	23	17		
10	4	26	9	Decrease in amplitude	Slight temporary decrease in amplitude
11	3	13	13	Decrease in amplitude	Temporary decrease in amplitude
12	7	36	14	Decrease in amplitude	Temporary decrease in amplitude
13	4	17	21	Decrease in amplitude	Temporary decrease in amplitude
Approximate average	4	23*.	17		

* Approximate average 18 mm. if dog 2 is excluded.

experiments have shown that after the pressure has recovered from the initial fall, the release in the occluded vessel causes a still greater rise in pressure, which shows that the supply to the left ventricle has been enhanced. The second rise in pressure is more abrupt than the original compensatory curve in the same animal, and the recovery from the secondary rise to the normal base line consumes less time. From this one might infer that the original compensatory rise is not initiated by an increase in the volume of blood passing through the unobstructed lung in one minute.

When the cord has been sectioned, with a subsequent loss of tone in the peripheral capillary bed, the compensatory rise in pressure does not occur, but if epinephrine is given to restore a certain amount of the loss, the pressure curve regains its usual contour, as in the dog with the

intact vagus and intact spinal cord. Most authorities believe that epinephrine has very little or no effect directly on the muscle of the heart. Extensive experimental work shows that epinephrine increases the pulmonary resistance by causing a constriction of the pulmonary arteries.

The compensatory rise in the carotid pressure in the dog after the cord has been sectioned following occlusion of the right pulmonary artery occurs only during the phase when the epinephrine is active. On the fall of the epinephrine curve, a compensatory rise in pressure does not occur if the right pulmonary artery is occluded. This shows definitely that the vasoconstrictors play a great part in helping to maintain a normal pressure after sudden occlusion of a part of the pulmonary arterial tree. Perhaps this mechanism is followed by a sudden dilatation of the remaining pulmonary capillaries, with a subsequent increase in the volume of blood to be sent to the left side of the heart. If this is true, then death may be caused by the inability of the remaining capillaries of the lungs to dilate or by inability of the right side of the heart to pump the required amount of blood through the lungs to the left ventricle.

Clinically, death might be expected after occlusion of a portion of the pulmonary artery if this occurred in a patient who had decompensation of the right side of the heart, or in a person with low blood pressure, especially a fat person of the emphysematous type. These considerations should be kept in mind in selecting cases of various pulmonary conditions for radical treatment in which ligation of branches of the pulmonary artery is contemplated. The treatment may be preventative in the type of cases of unilateral pulmonary embolism about which we have spoken. When this acute accident occurs, immediate forceful circulatory stimulation may carry the patient over the period of circulatory collapse of the systemic system until the pulmonary system can increase the volume lost in the occluded lung.

CONCLUSIONS

1. Occlusion of a branch of the pulmonary artery causes a temporary decrease in the carotid blood pressure in the otherwise normal dog.

2. The recovery from the fall in the carotid blood pressure after occlusion of one half of the pulmonary artery requires from ten to thirty seconds.

3. Occlusion of one half of the pulmonary artery in a dog when the spinal cord has been sectioned causes death.

4. The vasoconstrictors of the sympathetic system play an important part in causing the compensatory rise in the carotid pressure after one half of the pulmonary artery has been occluded.

5. Occlusion of from 75 to 100 per cent of the pulmonary artery causes death.

RETURN OF GASTRIC ACIDITY AFTER SUBTOTAL GASTRECTOMY AND DOUBLE VAGOTOMY

PHILIP F. SHAPIRO, M.D.

AND

BENJAMIN N. BERG, M.D.

NEW YORK

One of the fundamental principles underlying the treatment of peptic ulcers is an attempt to control gastric acidity. This idea is based on the assumption that the presence of hydrochloric acid is an important contributory factor in the etiology of ulcers.[1] As a result, various surgical measures are employed to reduce the acidity of the gastric contents. Simple procedures, such as gastro-enterostomy [2] and pyloroplasty,[3] afford only a temporary neutralization of gastric acidity and the development of recurrences and jejunal ulcers after these operations is attributed largely to the persistence of hyperchlorhydria. In order to achieve more lasting cures subtotal gastrectomy is advocated [4] as a method which provides for a permanent lowering of gastric acidity by interfering with the normal mechanism of acid secretion.

According to the present concept of the physiology of the stomach, acid is secreted normally in four phases. The first is the cephalic phase

1. Lindau, A., and Wulff, H.: The Peptic Genesis of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. 53:621, 1932. Hauser, G.: Die peptischen Schädigungen des Magens, des Duodenums und der Speiseröhre und das peptische postoperative Jejunalgeschwür, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4.

2. Berberich, J.: Nach Untersuchungen von Gastroenterostomien wegen Ulcus ventriculi und Ulcus duodeni, unter besonderer Berücksichtigung der Röntgendiagnostik, Beitr. z. klin. Chir. 119:194, 1932. Lewisohn, R., and Feldman, R. H.: Failure of Gastroenterostomy to Effect a Decisive Reduction in Gastric Acidity, Ann. Surg. 82:925, 1925.

3. Finney, J. M., and Friedenwald, J.: Thirteen Years' Experience with Pyloroplasty, Surg., Gynec. & Obst. 18:273, 1914.

4. Finsterer, H.: Die chirurgische Behandlung des Magens und Zwölffingerdarmgeschwüres und seiner Komplikationen, Ergebn. d. ges. Med. 15:431, 1930-1931.

which is controlled by the vagi. This corresponds to the appetite juice or psychic secretion described originally by Pavlov[5] in dogs and later by Carlson[6] in man. In the second or gastric phase, mechanical and chemical stimuli and secretagogues derived from food excite secretion.[7] In addition, according to Edkins,[8] during this phase a hormone, "gastrin," is liberated by the antrum and pylorus which stimulates the secretion of acid by the glands of the fundus. However, the existence of a specific gastric hormone is doubtful.[9] In the third or intestinal phase gastric secretion is prolonged by reflex stimuli originating[10] in the small intestine during the process of digestion. The fourth phase is the period of interdigestive, basal or continuous secretion. This secretion is probably a manifestation of vagus activity.[11]

From the surgical standpoint it is impossible to exclude the intestinal and continuous phases, but the first and second periods are amenable to modification. Attempts to reduce the psychic phase by dividing the vagi above or below the diaphragm have been unsuccessful. In dogs, Hartzell[12] found a reduction in acid after supraphrenic double vagotomy, but two years later Vanzant,[13] working with the same animals, reported that the acid had returned to normal values. Others[14] have

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5. Pavlov, L. P.: The Work of the Digestive Glands, London, Griffin & Company, 1910, p. 101.

6. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916, p. 235.

7. (a) Ivy, A. C.: Rôle of Hormones in Digestion, Physiol. Rev. **10**:282, 1930. (b) Lim, R.; Ivy, A. C., and McCarthy, J. E.: Gastric Secretion by Local Stimulation, Quart. J. Exper. Physiol. **15**:12, 1925. (c) Sawitsch, W., and Zeljony, G.: Zur Physiologie des Pylorus, Arch. f. d. ges. Physiol. **150**:128, 1913.

8. Edkins, J. S.: The Chemical Mechanism of Gastric Secretion, J. Physiol. **34**:133, 1906.

9. (a) Ivy.[7a] (b) Tomaszewski, Z.: Ueber die chemischen Erreger der Magendrüsen, Arch. f. d. ges. Physiol. **170**:260, 1918; **171**:1, 1918. (c) Priestley, J. T., and Mann, F. C.: Gastric Acidity with Special Reference to the Pars Pylorica and Pyloric Mucosa: An Experimental Study, Arch. Surg. **25**:395 (Aug.) 1932.

10. Ivy, A. C.: The Intestinal Phase of Gastric Secretion, Quart. J. Exper. Physiol. **15**:55, 1925.

11. Carlson,[6] p. 245.

12. Hartzell, J. B.: The Effect of Vagus Section on Gastric Acidity, Am. J. Physiol. **91**:161, 1929.

13. Vanzant, F. R.: Late Effects of Section of Vagus Nerves on Gastric Acidity, Am. J. Physiol. **99**:375, 1932.

14. (a) McCrea, E. D.; McSwiney, B. A., and Stopford, J. S.: The Effect on the Stomach of Section of the Vagus Nerves, Quart. J. Exper. Physiol. **16**:195, 1926. (b) Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929, p. 216. (c) Friedenwald, J., and Feldman, M.: Experimental Studies on the Effect of Section of the Vagus Nerve on Gastric Secretion, Arch. Int. Med. **49**:234 (Feb.) 1932.

also observed the return of gastric acidity after section of the vagi in animals. In man [15] division of one or both vagi produces only a transient decrease in gastric acidity.

Various types of operations on the stomach have been devised with the purpose of altering the second phase of gastric secretion. Side-tracking procedures and pyloroplasties have only a transient effect, which depends largely on the degree of neutralization of the gastric contents by regurgitated intestinal fluids. The more radical operation of subtotal gastrectomy aims to eliminate the second phase by removing the so-called hormone-elaborating portion of the stomach (antrum and pylorus). This is an effort directed toward modification of the mechanism of gastric secretion rather than simple neutralization of acidity.

The results of a number of experimental investigations in dogs indicate that resection of the pylorus and antrum has no permanent influence on gastric acidity. Smidt [16] studied the secretions obtained from Pavlov pouches in dogs after the Billroth I and II types of gastric resections. He found that the amount of secretion was diminished and the duration of the response to a test meal shortened, and ascribed this result to the absence of the second phase. However, the percentage of hydrochloric acid remained practically unchanged. In his conclusions he stated that it was impossible to attain complete "anacidity," owing to the fact that the psychic phase and reflex secretion remained unaffected. Enderlen and Zuckschwerdt,[17] having observed high acid values in the gastric contents of two patients many years after radical resection of the stomach, repeated Smidt's experiments, and studied the secretions from the pouches for longer periods of time. After four months their results were similar to those reported by Smidt. However, one year afterward the same animals showed a complete return of the second phase. As a matter of fact, frequently the quantity of secretion was greater and the duration of the response was longer than before resection. Again the percentage of hydrochloric acid was unchanged. They concluded that removal of the pylorus disturbed temporarily the second phase of secretion, but that a readjustment took place whereby the small intestine took over the function

15. Pieri, G., and Tanferna, U.: Effetti della resezione del vago sulla secrezione gastrica dell'uomo, Riforma med. **46**:323, 1930.

16. Smidt, H.: Experimentelle Studien am nach Pawlow isolierten kleinen Magen, über die sekretorisch Arbeit der Magendrüsen nach den Resektionen Billroth I und II, sowie nach der Pylorusausschaltung nach von Eiselsberg, Arch. f. klin. Chir. **125**:26, 1923.

17. Enderlen, E., and Zuckschwerdt, L.: Die Erregung der Magensaftsekretion nach Resektion des Antrum-Pylorusteils des Magens, Deutsche Ztschr. f. Chir. **232**:290, 1931.

of the pylorus as the stimulus for secretion by the fundus. London[18] found a temporary depression in gastric acidity after removal of the antrum and pylorus in dogs, and attributed the result to neutralization by regurgitated alkaline duodenal secretions. One month after resection he noted that the acidity of the gastric contents had returned to normal values, and reexamination of the same animals one year and three years later revealed that the chemistry of the gastric secretions was unaltered. In his animals, jejunal ulcers occurred practically always at the site of anastomosis between the fundus and jejunum. Portis and Portis[19] studied gastric secretion for several months after subtotal gastrectomy in dogs with Pavlov pouches. These investigators found no appreciable changes in the acidity of the secretion obtained from the pouch; in the main stomach no free hydrochloric acid was present, owing to neutralization by intestinal fluids, but the combined acidity was high. Recently, Priestley and Mann[9c] reported no change in gastric acidity after extirpation of the pars pylorica, and found no evidence of a humoral mechanism originating in the pyloric mucosa in dogs equipped with pyloric and totally transplanted fundic pouches.

In man, the results of investigations concerning gastric secretion after subtotal resection are difficult to interpret and inconclusive, owing to the unsatisfactory manner in which the studies have been conducted.[20] The reports[21] are based on the results obtained from a single gastric analysis after the administration of a test meal. Often the type of test meal and the time of extraction are not recorded. As a rule, the interval between the operation and the estimation of gastric acidity is not mentioned. The motility of the fundic remnant, the position of the tip of the aspiration tube as observed by fluoroscopy and the amount of regurgitation as determined by the presence of bile and pancreatic

18. London, E. S.: Experimentelle Physiologie und Pathologie der Verdauung, Berlin, Urban & Schwarzenberg, 1925, p. 157.

19. Portis, S. A., and Portis, B.: Effects of Subtotal Gastrectomy on Gastric Secretion, J. A. M. A. **86**:836 (March 20) 1926.

20. (*a*) Katsch, G.: Pathologische Physiologie des Magensaftes und des Magenchemismus, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 3, p. 1118. (*b*) Goetze, O.: Die Motilität und Sekretion des operierten Magens, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, vol. 3, p. 1199.

21. Schur, H., and Plaschkes, G.: Die Bedeutung der Funktion des Antrum pylori für die Magen Chirurgie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**:795, 1914-1915. Lorenz, H., and Schur, H.: Unsere Erfahrungen über den Wert der Antrumresektion bei der Behandlung des Ulcus pepticum, Arch. f. klin. Chir. **119**:219, 1922. Smidt, H.: Ueber Magenresektion und Magenchemismus, ibid. **130**:307, 1924. Lewisohn, R., and Ginzburg, L.: Relation of Post-Operative Achlorhydria to Cure of Gastric and Duodenal Ulcers, Surg., Gynec. & Obst. **47**:493, 1928. Louria, H. W.: The Surgical Treatment of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **47**:493, 1928.

enzymes in the gastric contents are details which are disregarded. Hence, the reports of "anacidity" after subtotal gastrectomy cannot be accepted without further, more complete studies. Klein [22] compared the acidity of the gastric contents following an Ewald meal, extracted after three quarters of an hour, with the acidity values following a Rehfuss meal, removed at frequent intervals during a period of three hours, in the same patient after subtotal removal of the stomach. In many instances he found that free acid appeared only after the first hour and then increased in amount in the succeeding specimens, demonstrating that acid values based on a single analysis after an Ewald meal are inadequate. Using the fractional method of analsyis, Klein reported that six months after gastric resection for duodenal ulcer 25 per cent of the patients showed anacidity (absence of free hydrochloric acid), 41 per cent hypo-acidity and 17 per cent hyperacidity. For the last group of cases with intractable hyperacidity he suggested division of the left vagus [23] in an attempt to eliminate the psychic phase and possibly the phase of continuous secretion which he believed to be the underlying factors in the failure to reduce acidity after subtotal gastrectomy. In a preliminary communication he reported anacidity in eight patients from two to six months after vagotomy. Goetze [20b] attributed the high acid values which were encountered in man, even after extensive gastric resections, to the influence of unalterable reflex stimuli.

According to Finsterer,[24] von Haberer [25] and Berg,[26] the increasing number of recurrences and jejunal ulcers which are being reported [27] after subtotal gastrectomy are due principally to inadequate removal of the stomach and persistent hyperacidity. In order to overcome the

22. Klein, E.: Gastric Secretion After Partial Gastrectomy, *J. A. M. A.* **89:** 1235 (Oct. 8) 1927.

23. Klein, E.: Left Vagus Section and Partial Gastrectomy for Duodenal Ulcer with Hyperacidity, Ann. Surg. **90:**65, 1929.

24. Finsterer, H.: *Beziehungen zwischen grösse der Magenresektion und Dauerheilung bei der Ulcus-Behandlung,* Beitr. z. klin. Chir. **147:**78, 1927.

25. von Haberer, H.: *Betrachtungen über Misserfolge nach Resektion wegen Magen und Duodenalgeschwüren,* Zentralbl. f. Chir. **57:**66, 1930; *Resektion zur Ausschaltung und rezidivierendes Jejunalucus,* Arch. f. klin. Chir. **146:**651, 1927.

26. Berg, A. A.: Mortality and Late Results of Subtotal Gastrectomy for Radical Cure of Gastric and Duodenal Ulcer, Ann. Surg. **92:**340, 1930.

27. Birgfeld, E.: *Ulcus pepticum jejuni nach Magenresektion,* Arch. f. klin. Chir. **137:**568, 1925. Balfour, D. C.: Recurring Ulcers Following Partial Gastrectomy, Ann. Surg. **88:**548, 1928. Hurst, A.: The Later Results of Partial Gastrectomy for Gastric and Duodenal Ulcer, Lancet **2:**680, 1928. Moynihan, B.: Some Problems in Gastric Surgery, Brit. M. J. **2:**1021, 1928. Starlinger, F.: *Das Rückfallsgeschwür nach Magenresektion wegen Ulcus ventriculi oder duodeni,* Arch. f. klin. Chir. **162:**564, 1930. Jaeger, F.: *Ueber die Ulcusrezidive nach Magenresektion,* Arch. f. klin. Chir. **161:**233, 1930.

hyperacidity of peptic ulcers and produce a permanent decrease in the output of hydrochloric acid, Finsterer [4] advocates the resection of at least two thirds of the stomach, so that a large area of secretory mucosa of the fundus is removed as well as the antrum and pylorus.

In view of the incomplete knowledge concerning the etiology of peptic ulcers in man, the necessity of lowering the acidity of the gastric juice in order to accomplish a cure is still open to question. As an example of the beneficial effects which may be secured without altering gastric acidity, the recent good results with mucin therapy may be cited. Brown and his co-workers [28] reported that the administration of mucin to patients with intractable ulcers results in marked improvement. They found that mucin in ordinary doses does not diminish gastric acidity appreciably when placed in the stomach after a two hour fractional test meal, followed by aspirations at frequent intervals of from four to seven hours.

Since significant changes in gastric acidity depend essentially on alterations in gastric secretion, the following investigation was undertaken in order to determine experimentally to what extent the secretory mechanism of the stomach can be modified by surgical intervention. The operation of subtotal gastrectomy and double vagotomy was chosen for this purpose, being considered the most radical procedure which could be employed surgically to alter the different phases of gastric secretion.

METHODS

Complete studies were made on eight dogs. All operations were performed under ether anesthesia and with strict asepsis. First, in order to observe gastric secretory activity unmodified by such factors as food, abnormal motility and intestinal regurgitation, a pouch derived entirely from the fundus of the stomach was constructed according to the technic described by Pavlov.[29] It is important to remember that the innervation of a Pavlov pouch remains intact. Then, from three to four weeks later, a subtotal gastrectomy was performed according to the Pólya [30] method and both vagi were divided. The distal two thirds of the stomach was resected beginning 3 cm. or more proximal to the incisura angularis and extending well beyond the pylorus. After closing the stump of the duodenum an end-to-side suture gastro-jejunostomy was done to reestablish the continuity of the stomach and small intestine. In order to determine whether the antrum and pylorus were removed completely, histologic examinations of the resected specimens and fundic remnants were made. It was found that although the site of demarcation between pyloric and fundic glands was variable in different animals, the resections were always carried well beyond the zone of transition, into the fundus.

28. Brown, C. F. G.; Cramer, S. P.; Jenkinson, E. L., and Gilbert, N. C.: Mucin Therapy for Peptic Ulcer, J. A. M. A. **99**:98 (July 9) 1932.

29. Pavlov,[5] p. 13.

30. Pólya, E.: Zur Stumpfversorgung nach Magenresektion, Zentralbl. f. Chir. **38**:892, 1911.

The anterior and posterior vagi were isolated on the abdominal portion of the esophagus and divided. In addition, the entire circumference of the esophagus was dissected free from all nerve filaments in order to insure complete interruption of smaller branches of the vagi. This was confirmed later at autopsy. Several anatomic dissections of the vagi were made, and the abdominal distribution of the nerves corresponded to McCrea's description.[31] At the lower end of the thoracic esophagus the right and left vagi break up into plexuses from which they emerge as two main trunks, an anterior and a posterior one. The nerves then pass through the esophageal opening in the diaphragm as two trunks, occasionally as three, rarely as four, and send their branches to the anterior and posterior surfaces of the stomach.

Gastric secretion was studied in the following manner. After the animals had been deprived of food for twenty-four hours, the fasting contents were aspirated. Then a test meal, consisting of from 100 to 150 Gm. of lean meat and 250 cc. of water, was given. Specimens were aspirated for analysis at hourly intervals for periods extending from four to seven hours after the administration of the test meal; the pouch was emptied of its contents each time but only samples sufficient for examination were withdrawn from the main stomach. Although there were individual variations in the secretory rates of different animals, there was a rough parallelism between the curve of acidity and the rate of secretion in the pouch of each dog before and after resection-vagotomy. This conformed with the previous observations of Pavlov,[32] Hollander and Cowgill [32a] and Portis and Portis.[19] As a rule, 10 cc. of juice was employed for titration; if this amount was not available, 5 cc. was used. Free, combined and total acid were determined in clinical units by titrating against tenth-normal sodium hydroxide, using Töpfer's reagent and phenolphthalein as indicators. Since in our experiments the hydrochloric acid was present principally as free acid in the pouch and in combination with proteins derived from meat and mucus in the main stomach, it was desirable for the sake of uniformity and simplicity to express the secretory activity of both by a common measure. For this purpose the value for total acidity was found to be most practical because the curves of acidity in the pouch and main stomach tended to run parallel to one another (see experimental results and charts). The gastric analyses were conducted in three stages: First, as a control, the response of the intact stomach to the test meal was established before any operative intervention. Then the acidity of the secretions of the pouch and main stomach was determined, usually from two to three weeks after the construction of the pouch. Finally, the secretory activity of the pouch and fundic remnant was observed within from five to seventeen days after resection-vagotomy and at frequent intervals afterward for periods extending from eight to twelve weeks.

In order to study vagus activity before and after double vagotomy, 2 mg. of atropine was injected subcutaneously at the time a test meal was given and a gastric analysis was made in the usual manner, the results being compared.

EXPERIMENTAL RESULTS

The accompanying tables and charts represent the results which were obtained in the eight experiments.

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31. McCrea, E. D.: The Abdominal Distribution of the Vagus, J. Anat. 59:18, 1924.

32. Pavlov,[5] p. 33.

32a. Hollander, F., and Cowgill, G. R.: Studies in Gastric Secretion, J. Biol. Chem. 91:151, 1931.

TABLE 1.—*Results of Test Meals in Dog 6; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Com-bined	Total
Fasting	8	14	22
1 hour	0	102	102
2 hours	0	110	110
3 hours	8	82	90
4 hours	30	30	60
5 hours	10	16	26

12 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	0	8	8	0	10	10
1 hour	50	8	58	0	52	52
2 hours	76	8	84	0	70	70
3 hours	48	10	58	0	50	50
4 hours	12	18	30	0	16	16

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	22	12	34	0	28	28
1 hour	122	12	134	0	96	96
2 hours	130	10	140	0	106	106
3 hours	112	10	122	18	54	72
4 hours	80	12	92	12	43	55
5 hours	34	16	50	0	24	24

33 Days After Resection-Vagotomy

	Pouch			Stomach		
Fasting	12	12	24	0	16	16
1 hour	100	10	110	0	80	80
2 hours	126	8	134	0	92	92
3 hours	90	12	102	0	60	60
4 hours	52	14	66	8	30	38
5 hours	18	14	32	4	16	20

2 Mg. of Atropine Before Resection-Vagotomy

	Pouch			Stomach		
Fasting	20	12	32	0	20	20
1 hour	34	10	44	0	30	30
2 hours	12	12	24	0	22	22
3 hours	10	16	26	0	24	24
4 hours	44	14	58	10	38	48
5 hours	86	10	96	25	20	45
6 hours	115	10	125	16	18	34

2 Mg. of Atropine 34 Days After Resection-Vagotomy

	Pouch			Stomach		
Fasting	16	10	26	0	18	18
1 hour	22	12	34	0	24	24
2 hours	10	12	22	0	16	16
3 hours	10	14	24	0	32	32
4 hours	48	12	60	10	42	52
5 hours	82	12	94	15	30	45
6 hours	108	12	120	12	20	32
7 hours	100	14	114	0	16	16

C. 7 Days After Resection-Vagotomy

	Pouch			Stomach		
Fasting	0	12	12	0	12	12
1 hour	26	10	36	0	30	30
2 hours	38	8	46	0	34	34
3 hours	18	10	28	0	20	20
4 hours	4	12	16	0	10	10

57 Days After Resection-Vagotomy

	Pouch			Stomach		
Fasting	18	12	30	0	14	14
1 hour	118	8	126	0	102	102
2 hours	130	8	138	0	108	108
3 hours	118	6	124	0	62	62
4 hours	84	10	94	12	32	44
5 hours	32	14	46	10	12	22

TABLE 2.—*Results of Test Meals in Dog 8; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Com-bined	Total
Fasting	0	16	16
1 hour	0	58	58
2 hours	0	82	82
3 hours	12	32	44
4 hours	0	14	14

26 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	8	12	20	0	12	12
1 hour	92	10	102	0	40	40
2 hours	94	10	104	0	52	52
3 hours	65	10	75	10	20	30
4 hours	40	12	52	0	18	18
5 hours	70	12	82	10	12	22
6 hours	88	10	98	6	14	20

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	24	12	36	0	24	24
1 hour	90	8	98	0	52	52
2 hours	100	8	108	0	86	86
3 hours	78	10	88	12	28	40
4 hours	60	10	70	24	10	34
5 hours	38	12	50	0	12	12

2 Mg. of Atropine, 27 Days After Resection-Vagotomy

	Pouch			Stomach		
Fasting	0	12	12	0	10	10
1 hour	0	8	8	0	8	8
2 hours	14	10	24	0	18	18
3 hours	34	10	44	0	36	36
4 hours	66	10	76	0	46	46
5 hours	97	8	105	6	34	40
6 hours	68	8	76	0	16	16
7 hours	50	10	60			

2 Mg. of Atropine Before Resection-Vagotomy

	Pouch			Stomach		
Fasting	30	14	44	0	22	22
1 hour	6	18	24	0	16	16
2 hours	28	12	40	0	24	24
3 hours	40	10	50	0	54	54
4 hours	100	10	110	0	60	60
5 hours	70	12	82	0	42	42
6 hours	30	14	44	0	18	18

60 Days After Resection-Vagotomy

	Pouch			Stomach		
Fasting	0	12	12	0	10	10
1 hour	93	7	100	0	50	50
2 hours	100	8	108	4	52	56
3 hours	84	8	92	0	30	30
4 hours	80	6	86	0	32	32
5 hours	60	8	68	0	12	12
6 hours	110	6	116	0	18	18
7 hours	90	8	98	0	14	14
8 hours	28	10	48			

C. 12 Days After Resection-Vagotomy

	Pouch			Stomach		
Fasting	16	14	30	0	14	14
1 hour	48	10	58	0	36	36
2 hours	44	12	56	0	28	28
3 hours	26	12	38	0	24	26
4 hours	52	10	62	0	30	30
5 hours	70	10	80	10	20	30

Two penetrating jejunal ulcers. One of them perforated, but was sealed by the tip of the quadrate lobe of the liver.

TABLE 3.—Results of Test Meals in Dog 1; Acidity in Clinical Units

A. Before Operation

	Stomach Free	Combined	Total
Fasting	0	10	10
1 hour	0	60	60
2 hours	18	82	100
3 hours	34	48	82
4 hours	20	42	62

54 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	22	14	36	0	22	22
1 hour	36	14	50	0	38	38
2 hours	54	14	68	0	52	52
3 hours	96	12	108	0	72	72
4 hours	120	14	134	12	86	98
5 hours	115	10	125	10	70	80
6 hours	96	14	110	8	44	52

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	0	8	8	0	12	12
1 hour	64	6	70	0	52	52
2 hours	110	4	114	14	80	94
3 hours	94	10	104	30	49	79
4 hours	69	12	81	18	46	64

2 Mg. of Atropine, 56 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	12	12	24	0	18	18
1 hour	0	10	10	0	10	10
2 hours	14	14	28	0	22	22
3 hours	34	14	48	0	42	42
4 hours	85	13	98	0	68	68
5 hours	94	12	106	10	80	90
6 hours	64	16	80	0	72	72

C. 12 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	7	8	15	0	12	12
1 hour	14	8	22	0	19	19
2 hours	43	13	56	0	36	36
3 hours	50	12	62	0	30	30
4 hours	45	15	60	0	28	28

68 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	8	12	20	0	22	22
1 hour	36	14	50	0	36	36
2 hours	59	16	74	0	66	66
3 hours	92	12	104	0	84	84
4 hours	112	12	124	10	88	98
5 hours	92	10	102	18	48	66
6 hours	42	12	54	10	30	40

33 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	5	16	21	4	20	24
1 hour	20	16	36	0	38	38
2 hours	32	14	46	0	52	52
3 hours	38	18	56	0	56	56
4 hours	52	16	68	6	54	60
5 hours	68	16	84	8	34	42

84 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	12	12	24	0	24	24
1 hour	40	12	52	0	50	50
2 hours	64	14	78	0	80	80
3 hours	98	10	108	0	96	96
4 hours	116	8	124	12	73	95
5 hours	107	8	115	20	30	50
6 hours	81	14	95	8	20	28

TABLE 4.—Results of Test Meals in Dog 2; Acidity in Clinical Units

A. Before Operation

	Stomach Free	Combined	Total
Fasting	0	12	12
1 hour	0	85	85
2 hours	0	92	92
3 hours	0	90	90
4 hours	8	56	64
5 hours	26	14	40

33 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	22	10	32	0	20	20
1 hour	116	8	124	0	54	54
2 hours	122	8	130	0	90	90
3 hours	118	10	128	18	58	76
4 hours	86	14	100	10	38	48
5 hours	36	14	50	4	16	20

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	0	16	16	0	12	12
1 hour	104	8	112	0	82	82
2 hours	108	10	118	0	94	94
3 hours	86	10	96	22	66	88
4 hours	48	12	60	30	24	54
5 hours	20	14	34	12	16	28

2 Mg. of Atropine, 34 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	8	14	22	0	14	14
1 hour	16	10	26	0	18	18
2 hours	34	10	44	0	30	30
3 hours	33	12	45	0	34	34
4 hours	24	14	38	0	30	30
5 hours	84	10	94	10	50	60
6 hours	100	8	108	12	26	38
7 hours	70	10	80			

2 Mg. of Atropine Before Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	16	16	32	0	22	22
1 hour	24	10	34	0	30	30
2 hours	40	10	50	0	38	38
3 hours	38	12	50	0	32	32
4 hours	28	14	42	0	20	20
5 hours	85	12	97	24	16	40
6 hours	95	10	105	38	16	54

54 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	10	14	24	0	12	12
1 hour	116	8	124	0	80	80
2 hours	125	5	130	0	90	90
3 hours	104	6	110	14	60	74
4 hours	54	8	62	16	24	40
5 hours	20	10	30	0	16	16

C. 12 Days After Resection-Vagotomy

	Free	Combined	Total	Free	Combined	Total
Fasting	0	12	12	0	10	10
1 hour	64	10	74	0	44	44
2 hours	75	10	85	0	58	58
3 hours	72	8	80	0	52	52
4 hours	54	10	64	0	35	35
5 hours	8	16	24	0	12	12

TABLE 5.—*Results of Test Meals in Dog 3; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Com-bined	Total
Fasting........................	0	12	12
1 hour........................	0	74	74
2 hours.......................	0	92	92
3 hours.......................	14	28	42
4 hours.......................	18	12	30

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	24	12	36	0	18	18
1 hour	90	8	98	0	70	70
2 hours	92	10	102	0	86	86
3 hours	58	12	70	8	32	40
4 hours	36	16	52	18	16	34

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	14	14	28	0	20	20
1 hour	0	6	6	0	12	12
2 hours	0	4	4	0	12	12
3 hours	6	18	24	0	20	20
4 hours	36	16	52	8	42	50

C. 12 Days After Resection-Vagotomy

Fasting	0	6	6	0	10	10
1 hour	10	12	22	0	26	26
2 hours	22	14	36	0	38	38
3 hours	16	14	30	0	26	26
4 hours	0	14	14	0	14	14

26 Days After Resection-Vagotomy

Fasting	6	8	14	0	12	12
1 hour	30	10	40	0	36	36
2 hours	38	12	50	0	46	46
3 hours	32	14	46	8	34	42
4 hours	12	14	26	0	16	16
5 hours	6	16	22	0	12	12

33 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	10	10	20	0	14	14
1 hour	76	12	88	0	62	62
2 hours	96	14	110	0	74	74
3 hours	82	12	91	0	82	82
4 hours	66	12	78	10	58	68
5 hours	32	12	44	8	40	48

2 Mg. of Atropine, 35 Days After Resection-Vagotomy

Fasting	16	10	26	0	20	20
1 hour	6	14	20	0	16	16
2 hours	10	12	22	0	20	20
3 hours	30	12	42	0	30	30
4 hours	41	14	55	0	48	48
5 hours	50	17	67			

47 Days After Resection-Vagotomy

Fasting	0	12	12	0	16	16
1 hour	81	14	95	0	60	60
2 hours	92	14	106	0	92	92
3 hours	80	10	90	6	66	72
4 hours	32	12	44	10	38	48
5 hours	20	14	34	10	16	26

59 Days After Resection-Vagotomy

Fasting	14	12	26	0	20	20
1 hour	92	10	102	0	66	66
2 hours	93	8	106	0	96	96
3 hours	78	12	90	12	66	78
4 hours	42	14	56	10	42	52
5 hours	14	14	28	8	20	28

On the sixty-third day generalized peritonitis developed from perforated jejunal ulcers

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TABLE 6.—*Results of Test Meals in Dog 4; Acidity in Clinical Units*

A. Before Operation

	Stomach		
	Free	Com-bined	Total
Fasting........................	0	14	14
1 hour........................	0	64	64
2 hours.......................	0	96	96
3 hours.......................	0	65	65
4 hours.......................	20	18	38

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	28	10	38	0	16	16
1 hour	82	8	90	0	62	62
2 hours	112	12	124	0	94	94
3 hours	100	10	110	0	68	68
4 hours	70	12	82	16	30	46
5 hours	42	12	54	10	14	24
6 hours	30	10	40	0	14	14

2 Mg. of Atropine Before Resection-Vagotomy

Fasting	32	12	44	0	26	26
1 hour	20	10	30	0	16	16
2 hours	4	8	12	0	14	14
3 hours	32	10	42	0	40	40
4 hours	72	10	82	0	66	66
5 hours	84	10	94	16	76	92
6 hours	92	8	100	24	74	98
7 hours	32	12	44	0	22	22

C. 17 Days After Resection-Vagotomy

Fasting	0	18	18	0	10	10
1 hour	12	16	28	0	20	20
2 hours	22	16	38	0	32	32
3 hours	32	14	46	0	40	40
4 hours	36	14	50	0	30	30
5 hours	14	12	26	0	16	16

31 Days After Resection-Vagotomy

	Pouch			Stomach		
	Free	Com-bined	Total	Free	Com-bined	Total
Fasting	10	16	26	0	18	18
1 hour	24	12	36	0	32	32
2 hours	52	12	64	0	58	58
3 hours	60	14	74	10	60	70
4 hours	72	16	88	8	38	46
5 hours	48	14	62	0	22	22

45 Days After Resection-Vagotomy

Fasting	8	16	24	0	24	24
1 hour	46	14	60	0	60	60
2 hours	82	16	98	0	82	82
3 hours	100	10	110	10	82	92
4 hours	102	12	114	12	52	64
5 hours	72	18	90	0	18	18

2 Mg. of Atropine, 47 Days After Resection-Vagotomy

Fasting	16	14	30	0	20	20
1 hour	12	12	24	0	16	16
2 hours	8	12	20	0	14	14
3 hours	14	16	30	0	34	34
4 hours	56	10	66	0	60	60
5 hours	96	14	110	0	80	80

60 Days After Resection-Vagotomy

Fasting	0	18	18	0	22	22
1 hour	64	16	80	0	66	66
2 hours	94	14	108	0	90	90
3 hours	104	18	122	0	94	94
4 hours	112	14	126	12	70	82
5 hours	76	14	90	0	20	20
6 hours	34	12	46			

TABLE 7.—Results of Test Meals in Dog 5; Acidity in Clinical Units

A. Before Operation

	Stomach Free	Combined	Total
Fasting	4	10	14
1 hour	0	85	85
2 hours	26	42	68
3 hours	26	20	46
4 hours	8	15	23

12 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	0	12	12	0	8	8
1 hour	22	13	35	5	65	70
2 hours	30	22	52	8	48	56
3 hours	39	20	59	0	18	18
4 hours	35	17	52	0	14	14

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	4	8	12	8	8	16
1 hour	12	15	27	0	82	82
2 hours	24	18	42	28	32	60
3 hours	6	12	18	20	26	46
4 hours	0	8	8	6	12	18

19 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	20	18	38	0	26	26
1 hour	40	14	54	5	70	75
2 hours	60	15	75	6	45	51
3 hours	64	18	82	0	21	21
4 hours	32	10	42	0	20	20

C. 5 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	6	8	14	0	8	8
1 hour	20	10	30	0	42	42
2 hours	4	8	12	0	18	18
3 hours	0	10	10	0	13	13
4 hours	0	10	10	0	8	8

2 Mg. of Atropine, 23 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	39	6	45	0	25	25
1 hour	0	18	18	0	23	23
2 hours	0	23	23	0	32	32
3 hours	4	25	29	0	40	40
4 hours	60	22	82	0	75	75
5 hours	35	25	60	0	45	45

TABLE 8.—Results of Test Meals in Dog 7; Acidity in Clinical Units

A. Before Operation

	Stomach Free	Combined	Total
Fasting	0	12	12
1 hour	0	72	72
2 hours	0	104	104
3 hours	18	46	64
4 hours	0	32	32

29 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	18	12	30	0	16	16
1 hour	52	10	62	0	52	52
2 hours	110	12	122	0	88	88
3 hours	118	10	128	0	40	40
4 hours	47	14	61	10	18	28
5 hours	20	12	32			

B. After Formation of Pavlov Pouch, Before Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	0	6	6	0	8	8
1 hour	100	12	112	0	64	64
2 hours	120	10	130	0	112	112
3 hours	94	16	110	15	60	75
4 hours	72	16	88	0	32	32
5 hours	24	18	42			

2 Mg. of Atropine, 32 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	10	8	18	0	14	14
1 hour	16	12	28	0	10	10
2 hours	16	10	26	0	22	22
3 hours	20	10	30	0	30	30
4 hours	30	12	42	0	36	36
5 hours	72	16	88	10	56	66

2 Mg. of Atropine Before Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	8	10	18	0	12	12
1 hour	26	14	40	0	24	24
2 hours	12	20	32	0	18	18
3 hours	0	16	16	0	14	14
4 hours	0	22	22	0	28	28
5 hours	68	16	84	12	62	74

42 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	0	10	10	0	12	12
1 hour	89	10	99	0	25	25
2 hours	102	8	110	0	50	50
3 hours	98	8	106	0	36	36
4 hours	40	12	52	0	20	20

C. 15 Days After Resection-Vagotomy

	Pouch Free	Combined	Total	Stomach Free	Combined	Total
Fasting	6	8	14	0	12	12
1 hour	32	12	44	0	26	26
2 hours	36	14	50	0	24	24
3 hours	30	12	42	0	32	32
4 hours	22	14	36	0	16	16

The formation of a Pavlov pouch had no appreciable effect on gastric secretion. Although from 25 to 30 per cent of the fundus was utilized for the construction of the pouch, after from two to three weeks the secretory response of the main stomach was practically the same as before the operation. The secretion from the pouch had a high acid titer.

After subtotal gastrectomy and double vagotomy a temporary diminution in acidity occurred in the secretions obtained from the main stomach remnant and the pouch in all of the animals, the acid values being approximately one-half the preoperative level. This phenomenon lasted approximately for from twelve to thirty-three days and represented a true depression in secretory activity because the acidity in the pouch was reduced approximately to the same extent as the acidity in the main stomach. It is important to note that the curves of total acidity in the pouch and main stomach tended to run a parallel course throughout the entire experiment and that one was practically always the counterpart of the other, the acid in the pouch being present nearly entirely as free hydrochloric acid and in the main stomach in the combined form. In the gastric remnant the acid values were usually lower than in the pouch, the difference depending probably on the degree of neutralization which resulted from the regurgitation of alkaline intestinal contents and the motility of the stomach.

Subsequently, the secretion of acid returned to its original preoperative level, the rate of recovery varying in different animals. In dogs 1, 2, 3, 4, 5 and 6 the acidity in the main stomach and pouch was found to have returned to its original values within from three to eight weeks after resection-vagotomy. Except for the fact that the maximum acidity in dogs 1 and 4 appeared from three to four hours after the test meal instead of in the second hour, the final curves of secretion could be very nearly superimposed on those obtained before operation (table 1 and charts 1 and 2). In dogs 7 and 8, after forty-two days and sixty days respectively, the acidity in the pouch was practically the same as before subtotal gastrectomy and vagotomy, but in the main stomach the total acidity remained somewhat lower than the original values (table 2 and charts 3 and 4). In dog 8, there was a secondary rise to maximum acidity in the fifth and sixth hours after the test meal in addition to the primary peak reached during the second and third hours. In these two animals the emptying time of the fundic remnant was extremely rapid and there was an unusual amount of regurgitation of intestinal contents, so that practically every sample contained large amounts of bile. The results of these experiments demonstrate that the total acidity in the main stomach after gastric resection depends on the motility of the fundic remnant, the
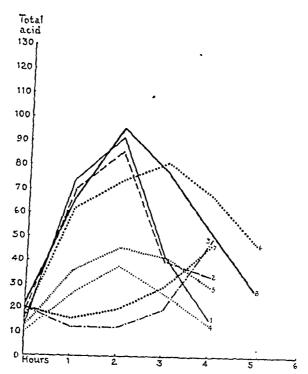
Chart 1 (dog 3).—Curves of total acidity in main stomach: *1*, before operation; *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, twelve days after resection and vagotomy; *5*, twenty-six days after resection and vagotomy; *6*, thirty-three days after resection and vagotomy; *7*, thirty-five days after resection and vagotomy, with injection of 2 mg. of atropine; *8*, fifty-nine days after resection and vagotomy.
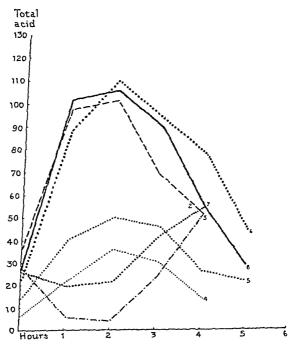
Chart 2 (dog 3).—Curves of total acidity in Pavlov pouch: *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, twelve days after resection and vagotomy; *5*, twenty-six days after resection and vagotomy; *6*, thirty-three days after resection and vagotomy; *7*, thirty-five days after resection and vagotomy, with injection of 2 mg. of atropine; *8*, fifty-nine days after resection and vagotomy.
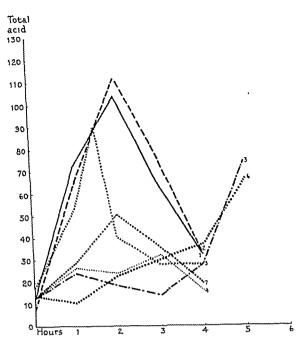
Chart 3 (dog 7).—Curves of total acidity in main stomach: *1*, before operation; *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, fifteen days after resection and vagotomy; *5*, twenty-nine days after resection and vagotomy (bile, 4 plus); *6*, thirty-two days after resection and vagotomy, with injection of 2 mg. of atropine; *7*, forty-two days after resection and vagotomy (bile, 4 plus).
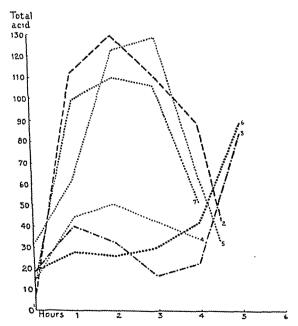
Chart 4 (dog 7).—Curves of total acidity in Pavlov pouch: *2*, after formation of Pavlov pouch; *3*, after formation of Pavlov pouch and injection of 2 mg. of atropine; *4*, fifteen days after resection and vagotomy; *5*, twenty-nine days after resection and vagotomy (bile in stomach, 4 plus); *6*, thirty-two days after resection and vagotomy, with injection of 2 mg. of atropine; *7*, forty-two days after resection and vagotomy (bile in stomach, 4 plus).

size of the stoma and the amount of neutralization by regurgitated intestinal fluids. The presence of secretory activity is shown by the good response of the pouch.

Atropine injected simultaneously with the administration of a test meal caused a marked depression in secretion in the pouch and main stomach in all of the animals. The inhibitory effect lasted from two to four hours and was just as marked after subtotal gastrectomy and double vagotomy as before. As the action of atropine wore off, secretion was resumed and the acid values gradually rose to a peak almost as high as the figures attained previously without atropine. Repeated injections prolonged the period of inhibition, but secretion always returned.

A rough parallelism between the curve of acidity and the rate of secretion occurred in the fundic remnant just as in the pouch. Since the magnitude of dilution of the gastric contents by the test meal was approximately the same before and after resection-vagotomy—the total volume of the test meal being alike under both conditions—changes in the rate of secretion were reflected roughly in the curve of acidity owing to the relatively constant dilution factor. Therefore, the return of acidity in the fundic remnant after resection-vagotomy was indirect evidence of the reestablishment of the secretory rate. This observation is particularly significant so far as the conditions in the fundic remnant are analogous to those which exist in man after subtotal gastrectomy.

Without trying to make any forced interpretation of the titration figures and curves presented, and fully aware of the variables and the limitations of the methods employed in this type of investigation, we believe that the sum total of three hundred acid titrations show definitely that sufficiently large amounts of acid occurred with a sufficient frequency to lead to the unavoidable conclusion that the physiologic mechanism of acid secretion was reestablished after resection-vagotomy.

During the progress of the experiments it was noted that the condition of the skin in the region of the Pavlov pouches was a good indicator of the amount of acid secreted at various stages of the investigation. As a rule, in dogs with Pavlov pouches, the skin adjacent to the external orifice is digested rapidly by the highly acid juice unless it is protected constantly by the application of neutralizing dressings, such as magnesium oxide powder and zinc oxide ointment. After gastric resection and vagotomy and concomitant with the temporary reduction in gastric acidity the neutralizing dressings could be dispensed with, and in cases in which digestion of the skin had occurred healing took place rapidly. However, after three or more weeks, with the gradual return of gastric acidity the skin began to break down again, and frequent neutralizing dressings had to be resumed in order to prevent extensive digestion of the abdominal wall.

At postmortem examination jejunal ulcers were found in two animals. In dog 3 there was a generalized peritonitis due to two perforated jejunal ulcers located about 8 cm. distal to the stoma. In addition, several smaller lesions were present. In dog 8 two marginal jejunal ulcers were found. One of them had perforated and the opening was sealed over by the tip of the quadrate lobe of the liver. Just distal to the suture line there was another superficial irregular jejunal ulcer. It is interesting to note that the gastric acidity in these animals was no higher than in the ones in which no ulcers developed. Others [33] have also reported the occurrence of jejunal ulcers in dogs after subtotal gastrectomy.

FACTORS CONCERNED IN THE RETURN OF GASTRIC ACIDITY AFTER SUBTOTAL GASTRECTOMY AND DOUBLE VAGOTOMY

The return of acidity after subtotal gastrectomy and double vagotomy is due to a number of factors which serve to maintain gastric secretion after the loss of the antrum and pylorus and division of the vagi.

First, section of the main branches of the vagi does not eliminate their influence on gastric secretory activity. This is demonstrated clearly by the studies with atropine which show that its pharmacologic action on the secretion of acid is practically the same after vagotomy as before. The vagi are parasympathetic nerves which terminate in the ganglionic plexuses of Meissner and Auerbach located in the wall of the stomach.[34] Kuntz [35] established the fact that these plexuses constitute an intrinsic reflex arc. Interruption of the continuity of the main vagus trunks cuts out the preganglionic fibers, but the postganglionic fibers remain intact. Atropine paralyzes the postganglionic mechanism of the parasympathetic nerves and arrests secretions which depend on central innervation. Its site of action is localized in the nerve endings or receptive substance and it is mutually antagonistic with pilocarpine.[36] This explains the phenomenon of atropine inhibition after section of the vagi. Since the entire intrinsic nervous mechanism of the stomach remains intact, it is evident that the phases of gastric secretion which are controlled by the vagi, namely the cephalic and

33. London.[18] Koennecke, W.: Experimentelle Untersuchungen über die Bedeutung des Pylorusmagens für die Ulcusgenese, Arch. f. klin. Chir. **120**:537, 1927. Ivy, A. C.: Personal communication to the authors.

34. McSwiney, B. A.: Innervation of the Stomach, Physiol. Rev. **11**:478, 1931.

35. Kuntz, A.: On the Occurrence of Reflex Arcs in the Myenteric and Submucous Plexuses, Anat. Rec. **24**:193, 1922.

36. Sollmann, T.: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1932, p. 389.

continuous phases, cannot be modified by vagotomy. Recently Klein[37] attempted to denervate transplanted gastric pouches by eliminating Auerbach's plexus, situated between the muscular layers of the wall of the stomach. However, it is practically impossible to denervate a pouch as long as the submucosa remains intact. Kuntz demonstrated that in the submucosa there are an enormous number of small ganglions and plexuses which send fibers to the muscularis mucosae, the glands in the mucosa and the gastric epithelium. The fibers which terminate in the epithelium are probably dendrites of neurons in the submucous plexus. The cells in the latter are probably of vagus origin, although some may be sympathetic. The histologic and pharmacologic studies of Ken Kuré and his co-workers[38] indicate that there are efferent parasympathetic fibers in some of the dorsal roots and other elements of the sympathetic nervous system which reach the stomach independent of the vagus. The splanchnic nerves, although predominantly inhibitory in nature, also carry excitatory fibers in them.[39] Obviously, division of the vagi does not affect these nerves.

Second, subtotal gastrectomy has only a temporary effect on the chemical phase of secretion. Although removal of the pylorus and antrum is accompanied by a reduction in acidity, the effect is a transient one and is followed by a return of acid secretion. Apparently, if a hormone is elaborated in this part of the stomach, its presence is not essential for the secretion of acid by the fundus. Local mechanical and chemical stimuli and secretagogues continue to act and contribute to the full recovery of the second phase.

Third, the intestinal phase remains unaltered and continues to exert an influence on secretion. The recent investigations of Crider and Thomas[40] indicate that reflex stimuli originating in the small intestine during digestion may be responsible for a larger proportion of the total gastric secretion than is manifest from previous studies. Moreover, after subtotal gastrectomy, the emptying time of the fundic remnant is shortened to one-half[19] and the influence of the intestinal phase manifests itself earlier than in the normal stomach.

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37. Klein, E.: Gastric Secretion: II. Studies in a Transplanted Gastric Pouch Without Auerbach's Plexus, Arch. Surg. **25**:442 (Sept.) 1932.

38. Kuré, Ken; Ichiko, Kin-Ichi, and Ishikawa, Kysusabura: On the Spinal Parasympathetic, Quart. J. Exper. Physiol. **21**:1, 1931. Kuré, Ken; Saegusa, Gen-Ichi; Kawaguchi, Ken, and Yamagata, Kenchi: On the Spinal Parasympathetic, ibid. **21**:103, 1931. Kuré, Ken; Ikeda, Ryoji; Ichika, Kin-Ichi, and Wada, Yasukiko: On the Spinal Parasympathetic, ibid. **21**:119, 1931.

39. Kuntz,[14b] p. 213.

40. Crider, J. O., and Thomas, J. E.: Influence of Certain Conditions in the Duodenum on the Rate of Secretion and Acidity of the Gastric Juices, Am. J. Physiol. **101**:25, 1932.

Fourth, the margin of reserve with respect to secretory surface area and the capacity of the glandular epithelium of the stomach to regenerate are factors which must be reckoned with in any attempt to diminish permanently by extensive gastric resection the amount of hydrochloric acid secreted by the fundus. Although exact quantitative studies have not been made, it is probable that the fundus, just like other secretory organs, such as the liver and pancreas, can accommodate itself to the extirpation of a large portion of its surface epithelium without any permanent diminution in the output of hydrochloric acid. The cytologic investigations of Griffini and Vassale [41] and of Ferguson [42] demonstrate the excellent regeneration of the gastric glands after the experimental removal of large areas of mucosa.

Finally, the results of tissue culture studies indicate that glandular epithelium, like other body tissues, tends to continue its functional activity when explanted. A pure strain of thyroid cells produces colloid morphologically identical with that found in the adult gland.[43] Kapel's [44] work indicates, on admittedly incomplete evidence, that embryonic gastric epithelium grown in vitro may secrete mucus and possibly enzymes. According to Kuntz, "secretion is an inherent function of gland cells, and constitutes a manifestation of their metabolic activity." Gastric secretion is not interrupted in the absence of nervous impulses, but continues subject only to the measure of control which is afforded by nonnervous factors.[45]

<div style="text-align:center">COMMENT</div>

Although it is recognized that due allowances must be made for differences in species, we believe that the results of our experiments are significant with respect to man because the bulk of our knowledge concerning the physiology of the stomach is based on observations on dogs, which have been verified in man. In investigations dealing with estimations of gastric acidity, it is always necessary to distinguish between results due to neutralization factors and actual alterations in secretory activity. In dogs this can be done with relative ease by studying the pure secretions in pouches. In man it is more difficult

41. Griffini, L., and Vassale, G.: Ueber die Reproduktion der Magenschleimhaut, Beitr. z. path. Anat. u. z. allg. Path. 3:428, 1888.

42. Ferguson, A. N.: A Cytological Study of the Regeneration of Gastric Glands Following the Experimental Removal of Large Areas of Mucosa, Am. J. Anat. 42:403, 1928.

43. Ebeling, A. H.: A Pure Strain of Thyroid Cells and Its Characteristics, J. Exper. Med. 41:337, 1925.

44. Kapel, O.: Einige Untersuchungen über das Verhalten des Epithels in Vitro, Arch. f. exper. Zellforsch. 8:35, 1929.

45. Kuntz,[14b] p. 218.

to dissociate the two because indirect methods must be employed. Earlier in the paper it was pointed out that the reports in the literature concerning gastric secretion in man after subtotal removal of the stomach for ulcer were inconclusive, owing to inadequate methods. Since one of the primary objects of gastric resection is to induce a permanent reduction in acidity and since the results of experimental investigations indicate that intrinsic compensatory mechanisms militate against any permanent modifications in the secretion of hydrochloric acid, it is necessary to reinvestigate the problem, using more accurate methods than have been employed heretofore.

A sufficient length of time must be allowed to elapse before it can be determined definitely whether any permanent modification of gastric secretion has developed after subtotal gastrectomy. Gastric analyses should be made at frequent intervals and according to the fractional method for periods extending from four to six hours after the administration of a uniform test meal. The presence of bile in specimens of gastric contents is presumptive evidence that there is a large admixture of intestinal fluids, and under such conditions the acid values are unreliable owing to neutralization factors. With a small remnant of fundus and a large stoma it is important to ascertain the position of the tip of the aspirating tube by fluoroscopic examination in order to make sure that it is not too close to the lumen of the intestine. The emptying time of the stomach must be known. In the presence of a test meal the total acidity is a better gage of the output of hydrochloric acid than the free acidity, and the estimation of total chlorides may give additional corroboratory information concerning the secretion of acid. In the complete absence of titratable hydrochloric acid the potential secretory function of the gastric remnant can be determined by the response to histamine. The term "anacidity" is confusing because it is used by different investigators to convey different meanings and should be replaced by more definite terms, such as achlorhydria and hypochlorhydria. In interpreting the results of analyses the factor of individual variation and the limitations of the methods employed must be considered constantly. Attention to details of the type just outlined will render it possible to evaluate properly the end-results of subtotal resection for peptic ulcer in man with respect to gastric acidity.

CONCLUSIONS

1. Subtotal gastrectomy and double vagotomy in dogs induce only a temporary reduction in gastric acidity, which is due principally to a transient decrease in the secretory activity of the fundic remnant. This is followed by a return of acidity and secretory function.

2. The stomach is endowed with highly efficient compensatory mechanisms which provide for the continuation of secretion of hydrochloric acid by the fundus after removal of the antrum and pylorus and section of the vagi.

3. The fact that division of the vagi does not abolish the inhibitory action of atropine indicates that the intrinsic postganglionic mechanism remains intact.

4. Jejunal ulcers develop not infrequently after subtotal resection in dogs.

5. It is important to distinguish between a diminution in gastric acidity which is due to neutralization and a change which represents a real decrease in secretory function.

6. There is no experimental proof or convincing clinical evidence to support the hypothesis that subtotal gastrectomy, even combined with vagotomy, is the operation of choice for the surgical cure of peptic ulcer in man on the basis that it provides for a permanent lowering in the secretion of hydrochloric acid and thus prevents the development of recurrences and jejunal ulcers.

ABSORPTION OF UREA FROM THE BLADDER

FREDERICK A. FENDER, M.D.

BOSTON

For over one hundred years speculation has occurred in regard to the permeability of the bladder wall to physiologic as well as foreign substances. The reason for again taking up the subject is that a possible clinical application arose that seemed to warrant investigation. In a patient of this clinic, following an injury that amounted to transection of the cervical cord a marked cystitis developed, a complication that persisted in spite of cystotomy and generous lavage of the bladder. With this, there developed an abnormally high nonprotein nitrogen content of the blood, though a high fluid intake and output had been maintained, and though the function of the kidneys as measured by phenolsulphonphthalein excretion was good. In a conversation with Dr. Frank Fremont-Smith of the Harvard Neurological Unit, the possibility of reabsorption from the bladder was suggested as responsible for this turn of events, and the inquiry outlined here was undertaken in an effort to evaluate this possibility.

Though it has been done in earlier papers, some of the salient experiments may be capitulated. It should be made clear that the following material and the bibliographic references represent only fragments of the bulk of the work on this subject. For brevity's sake, only more prominent contributions have been included.

Kaupp,[1] as a medical student in 1856, compared specimens of his own urine voided hourly through the day with specimens retained for periods of twelve hours. Over a considerable period of time the retained urine was consistently lower in urea, water, sodium chloride, phosphates and sulphates. Kaupp believed this to be due to reabsorption of these into the blood stream.

Treskin,[2] in 1872, placed previously analyzed material into the bladders of dogs and reexamined specimens after the passage of various periods of time. Changes in the urea content, as well as in the volume, chlorides and specific gravity were thought attributable to interchange with the blood by diffusion through the bladder wall.

Ashdown [3] used three methods to establish his belief that the normal bladder is capable of absorption: He was able to poison dogs with

1. Kaupp, W.: Arch. f. physiol. Heilk. **15**:125, 1856.
2. Treskin: Arch. f. d. ges. Physiol. **5**:374, 1872.
3. Ashdown, H. H.: J. Anat. & Physiol. **21**:299, 1886-1887.

strychnine and other solutions introduced via a catheter; iodine identified by starch, was found to pass from the proximal ends of divided ureters after introduction into the bladder, a solution of urea decreased in concentration on remaining in the bladder.

Gerota,[4] in 1897, made observations on urine that had remained in the bladder after division and ligation of the ureters and found changes which he ascribed to absorption through a permeable bladder wall.

In the same year, Morro and Gabelein,[5] investigating the matter because of a possible clinical application, found that "mentionable" quantities of a number of substances introduced into the bladder of dogs were absorbed. Of salt, sugar, urea, boric acid, phenol, alcohol, potassium chloride, cocaine, quinine and morphine, only morphine failed of absorption. They concluded that great care should be taken in the clinical employment of cocaine (advice that has gone unheeded with fatal result since), and that phenol should not be used.

Cohnheim,[6] in 1901, closed the discussion for some years with a paper in which he reported work of a similar nature with a different outcome. He likewise, introduced "physiologic" and "nonphysiologic" or toxic material into the bladders of dogs, examining the first chemically before and after remaining in the bladder, and noting the systemic effects of the second. He concluded that the bladder wall is not a permeable membrane, even for water, unless a noxious substance has previously altered its native qualities.

Resuming investigation of the subject in this country, Macht,[7] in 1918, reported an interesting series of experiments on male dogs, taking as the criteria for his results systemic changes wrought by suitable substances placed in the bladder. Thus, the residual inhibitability of the heart by vagus stimulation was taken as evidence of atropine absorption, and fatal poisoning as indicative of absorption of nicotine. This investigator perhaps was the first to discriminate carefully between the respective rôles of the bladder and posterior urethra in absorption. He found little or no evidence of absorption of the three groups of substances studied, alkaloids (atropine, pilocarpine and nicotine), antiseptics (phenol and cresol) and anesthetics (cocaine and alypin), unless these were allowed to come into contact with the urethra. In this case, evidence of absorption usually appeared promptly. Even potassium cyanide, in doses of from 100 to 250 mg. failed of effect until it acted on the posterior urethra.

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4. Gerota, D.: Arch. f. Physiol., 1897, p. 428.
5. Morro and Gabelein: Ztschr. f. klin. Med. **32**:12, 1897.
6. Cohnheim, O.: Ztschr. f. Biol. **41**:331, 1901.
7. Macht, D. I.: J. Urol. **2**:43 (Feb.); 211 (June) 1918.

Two years later, Shoji,[8] using cats and rabbits, introduced physiologically-significant concentrations of salt solution. In addition to changes in the amounts of salt, the author noted absolute shifts in the water by observing changes in concentration of a substance (hemoglobin) in colloidal suspension. His results may be summarized thus: With 1 per cent solution, the water and salt remained the same; with 0.5 per cent, water was absorbed, and salt remained the same; with solutions of 0.25 per cent or less, there was a decrease in water and an increase in salt; in solutions of 2 per cent, the reverse of this took place. Shoji held it proved that the bladder epithelium is permeable to water and sodium chloride.

Mann and Magoun,[9] in 1923, assumed that absorption of small quantities of material can take place after recovering, from the proximal ends of divided ureters, phenolphthalein and indigo carmine previously introduced into the bladder.

The following year, Vickers and Marshal[10] found definite diminution in urea and salt left in the rabbit's bladder. A disproportionately great loss of urea with the use of 0.7 molar solution was thought due to injury of the bladder wall by the drug.

In 1925, Schönfeld and Müller[11] investigated absorption from the bladder in man from a clinical point of view, following deaths from the use of derivatives of cocaine. They found evidence of absorption of pilocarpine and tuberculin.

In spite of contradictions appearing in the foregoing, it seems reasonable, after analysis, to make several assumptions:

1. Excluding all part of the urethra, the bladder wall is slightly permeable to substances found normally in the urine, specifically, water, sodium chloride and urea.

2. Other substances may be transmitted to a slight extent, but the possibility of alterations in the normal physiology of the wall must be associated with any such consideration.

3. Trauma or inflammation grossly increases the permeability of the bladder.

These seem fair conclusions to draw. They do not embrace the whole question, but more specific conclusions involve considerable differences of opinion and cannot be said to rest on impregnable experimental work. The variations in results admit of several possible explanations that will not be discussed here, except to say that failure to

8. Shoji, R.: J. Physiol. **54:**239 (Dec.) 1920.
9. Mann, F. C., and Magoun, J. A. H.: A. J. M. Sc. **166:**96, 1923.
10. Vickers, J., and Marshal, E. D.: Am. J. Physiol. **70:**607, 1924.
11. Schönfeld, W., and Müller, W. G.: München. med. Wchnschr. **72:**291 (Feb. 20) 1925.

confine substances to the bladder alone and trauma inherent in the method must have affected the results in several cases.

The method that my co-workers and I used in our approach to the subject is a crude one, purposely so. Our interest was clinical, rather than physiologic, and designed to answer a specific question within certain limits. And the method, as shown by the negative control experiments, is suitable within those limits.

METHOD

Cats were anesthetized with sodium amytal, 7 cc. of a 1 per cent solution per kilogram of body weight being given intraperitoneally from twenty to thirty minutes before operation. At operation, a midline incision was made. The intestines were walled off with cotton moistened with warm physiologic solution of sodium chloride. The neck of the bladder was grasped in a fine snap. The ureters were tied and severed close to the bladder. Urine was withdrawn from, and substances introduced into, the bladder by means of a needle, the puncture being made in an avascular region, and the needle remaining in place throughout in order to avoid additional trauma. Specimens of blood were withdrawn from the vena cava from time to time with a fine needle, about 1.5 cc. being taken for each analysis. The cava was entered obliquely, and a warm, moist cotton pledget, laid gently against the puncture wound, sufficed to control hemorrhage. Care was taken to avoid irrelevant trauma, the bladder and other viscera being covered with cotton moistened with warm physiologic solution of sodium chloride during the extent of the experiment. The bladder was never distended to any extent by introduction of solutions, the amount introduced usually approximating that of urine withdrawn, and the injection being made very gently. Surgical solution of chlorinated soda (Dakin's solution) used was freshly made in each case. In the one instance in which it seemed that an active flow was not maintained in the vena cava, the whole experiment was discarded.

EXPERIMENTAL WORK

Specimens of blood from the vena cava were examined for non-protein nitrogen after the introduction of urea into the bladder, with and without previous irritation of the bladder mucosa by surgical solution of chlorinated soda. Two control experiments were carried out in which warm physiologic solution of sodium chloride was used in place of urea following irritation by the surgical solution. The pertinent experiments were those in which 10 per cent urea was placed in the bladder, and the experiment concerns these chiefly. One other experiment is reported to show that absorption readily takes place without previous irritation when a strong (50 per cent) solution is introduced. The specimens of heart blood were taken toward the end of each experiment to serve as a check on systemic absorption. Protocols of typical experiments follow:

Effect of Concentrated Urea.—Fifty per cent urea was introduced into the bladder without previous irritation of the mucosa. The animal used was a female cat weighing 3 Kg., which was anesthetized with 21 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:05	Initial specimen of blood taken	57
:07	Urine withdrawn, 25 cc.	
:10	Urea introduced, 25 cc., 50 %	
:15	Blood specimen II (cava)	62
:45	Blood specimen III (cava)	80
1:15 {	Blood specimen IV (cava)	154
{	Blood specimen V (heart)	100
1:45 {	Blood specimen VI (cava)	128
{	Blood specimen VII (heart)	161

The bladder was incised at the conclusion of the experiment; it showed moderate injection. No hemorrhages were in evidence. A marked rise in blood nonprotein nitrogen was seen. This concentration of urea doubtless invalidates normal function of the bladder.

Experiment I.—Ten per cent urea was introduced into the bladder without previous irritation. The animal used was a male cat weighing 3.8 Kg., which was anesthetized with 26.5 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
:00	Operation carried out	
:05	Initial specimen of blood taken	42
:09	Urine withdrawn, 15 cc.	
:10	Urea introduced, 25 cc., 10 % (slowly)	
:15	Blood specimen II (cava)	47
:45	Blood specimen III (cava)	45
1:15 {	Blood specimen IV (cava)	44
{	Blood specimen V (heart)	43
1:45 {	Blood specimen VI (cava)	42
{	Blood specimen VII (heart)	43

The incised bladder showed no apparent inflammation.

Chart 1.—Curves obtained in experiments I and II in which 10 per cent urea was introduced into the bladder without irritation of the mucosa.

EXPERIMENT II.—Ten per cent urea was introduced into the bladder without previous irritation (as in the foregoing experiments). The animal used was a male cat weighing 3.4 Kg., which was anesthetized with 24 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
: 00	Operation carried out	
: 05	Initial specimen of blood taken	34
: 07	Urine withdrawn, 49 cc.	
: 10	Urea introduced, 35 cc., 10 %	
: 15	Blood specimen II (cava)	33
: 45	Blood specimen III (cava)	36
1 : 15 {	Blood specimen IV (cava)	35
	Blood specimen V (heart)	38
1 : 45 {	Blood specimen VI (cava)	35
	Blood specimen VII (heart)	39

The incised bladder showed no apparent inflammation.

The two foregoing experiments are taken to show that absorption of urea could not be detected by our method when the 10 per cent solution was introduced into the bladder without previous irritation.

EXPERIMENT III.—Ten per cent urea was introduced into the bladder following irritation for five minutes with surgical solution of chlorinated soda. The animal used was a female cat weighing 3.1 Kg., which was anesthetized with 22 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
: 00	Operation carried out	
: 03	Initial specimen of blood taken	35
: 09	Urine withdrawn, 75 cc.	
: 10	Surgical solution of chlorinated soda introduced, 30 cc.	
: 15	Surgical solution of chlorinated soda withdrawn	
: 17	Urea introduced, 30 cc., 10 %	
: 22	Blood specimen II (cava)	Lost
: 52	Blood specimen III (cava)	59
1 : 22 {	Blood specimen IV (cava)	64
	Blood specimen V (heart)	55
1 : 52 {	Blood specimen VI (cava)	60
	Blood specimen VII (heart)	53

The incised bladder showed marked injection of the mucosa.

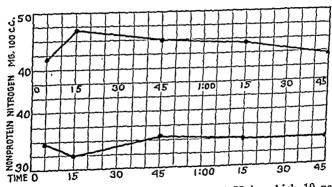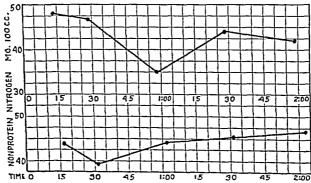Chart 2.—Curves obtained in experiments III and IV in which 10 per cent urea was introduced into the bladder following irritation of the mucosa with surgical solution of chlorinated soda.

EXPERIMENT IV.—Ten per cent urea was introduced into the bladder following irritation for five minutes with surgical solution of chlorinated soda. The animal used was a male cat weighing 4.5 Kg., which was anesthetized with 30 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
: 00	Operation carried out	
: 04	Initial specimen of blood taken	47
: 10	Urine withdrawn, 23 cc.	
: 11	Surgical solution of chlorinated soda introduced, 25 cc.	
: 15	Surgical solution of chlorinated soda withdrawn	
: 18	Urea introduced, 25 cc., 10 %	
: 23	Blood specimen II (cava)	52
: 53	Blood specimen III (cava)	84
1 : 23 {	Blood specimen IV (cava)	77
{	Blood specimen V (heart)	74
1 : 53 {	Blood specimen VI (cava)	89
{	Blood specimen VII (heart)	84

The incised bladder showed moderate injection of the mucosa.

The last two experiments, flanked by controls, are considered the significant experiments in this series. Two control experiments, in addition to I and II, were made as follows:

EXPERIMENT V.—The anesthetic, operative procedure and irritation by surgical solution of chlorinated soda were carried out as in the preceding experiments. Warm physiologic solution of sodium chloride was used instead of urea. The animal used was a male cat weighing 3 Kg., which was anesthetized with 21 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
: 00	Operation carried out	
: 14	Initial specimen of blood taken	48
: 15	Urine withdrawn, 10 cc.	
: 16	Surgical solution of chlorinated soda introduced, 10 cc.	
: 21	Surgical solution of chlorinated soda withdrawn	
: 23	Saline introduced, 10 cc., warm	
: 28	Blood specimen II (cava)	47
: 58	Blood specimen III (cava)	35
1 : 28 {	Blood specimen IV (cava)	44
{	Blood specimen V (heart)	48
1 : 58 {	Blood specimen VI (cava)	42
{	Blood specimen VII (heart)	43

The incised bladder showed slightly reddened and inflamed mucosa. No hemorrhage was in evidence.
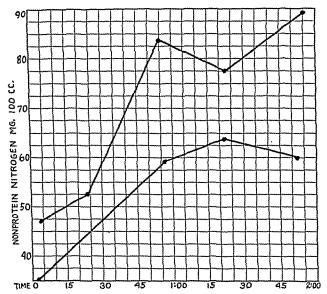
Chart 3.—Curves obtained in control experiments V and VI in which irritation was produced by surgical solution of chlorinated soda and physiologic solution of sodium chloride replaced the urea.

EXPERIMENT VI.—The procedure was the same as in experiment V. The animal used was a female cat weighing 4.2 Kg., which was anesthetized with 29 cc. of 1 per cent amytal.

Time	Comment	Blood nonprotein nitrogen, Mg. per 100 Cc.
: 00	Operation carried out	
: 17	Initial specimen of blood taken	44
: 18	Urine withdrawn, 5 cc.	
: 20	Surgical solution of chlorinated soda introduced, 15 cc.	
: 25	Surgical solution of chlorinated soda withdrawn	
: 26	Saline introduced, 15 cc.	
: 31	Blood specimen II (cava)	39
1 : 01	Blood specimen III (cava)	44
1 : 31 {	Blood specimen IV (cava)	46
{	Blood specimen V (heart)	52
2 : 01 {	Blood specimen VI (cava)	47
{	Blood specimen VII (heart)	46

No inflammation of the incised bladder was evident.

COMMENT

It will be noticed that the second specimen of blood is taken five minutes after the significant maneuver in each case, and that the third, fourth and sixth follow at thirty minute intervals.

Additional experiments, patterned after the experiment reported, seemed, likewise, to show that this very strong solution of urea (50 per cent) so altered the bladder wall that absorption took place readily.

On the other hand, 10 per cent urea does not produce these changes to any such extent, and in this concentration the substance is not absorbed in quantities recognizable by our method. Following the inflammatory changes produced by surgical solution of chlorinated soda, however, there is a considerable rise (an average of 65 per cent in the two experiments).

The situation seems in some respects analogous to that encountered in the case of our patient, and we wonder whether absorption from an inflamed, imperfectly drained bladder may not have played an etiologic rôle in the development of his uremia.

CONCLUSIONS

1. The inflamed bladder mucosa transmits urea in quantities sufficient to raise the nonprotein nitrogen of the blood appreciably.

2. This mechanism may play an etiologic rôle in the development of uremia by patients having neurologically incapacitated bladders.

TREATMENT OF INFECTED WOUNDS OF THE BRAIN WITH BACTERIAL FILTRATES

J. R. B. BRANCH, M.D.

A. A. LEMPERT
AND
R. S. LYMAN, M.D.
SHANGHAI, CHINA

A number of soldiers were brought to the Chinese Red Cross General Hospital with wounds of the head sustained in the recent Sino-Japanese hostilities at Shanghai. All these wounds were infected. During the first few weeks of this period the outcome in each case seemed to be determined by the course of the infection. The wounds were treated in a routine manner by irrigation and dressings with surgical solution of chlorinated soda. . During the last few weeks bacterial filtrates were used instead of the solution as a further means of controlling the infection. Eight of the last ten patients admitted with open infected wounds of the head involving the brain received treatment with filtrates. We herewith report the results of this treatment.

PROCEDURE

Smears and cultures were made from the wounds as soon as possible after the admission of the patients to the neurosurgical division. The surgical condition was then inspected, and the need of operation was decided on, with the help of a roentgenogram. If no operation seemed necessary, the use of surgical solution of chlorinated soda was discontinued and dressings soaked with polyvalent streptococcus-staphylococcus filtrate were applied. For the first day or so these dressings were changed several times; they were changed less frequently as time went on. If necessary, irrigation was carried out with a sterile physiologic solution of sodium chloride at the time when the dressings were being changed. In cases in which an operation seemed desirable, usually for the removal of fragments of bone or to provide adequate exposure of an infected area, surgical measures were carried out first; the wounds were dressed and drained with gauze moistened with bacterial filtrate; further applications of filtrate were made just as in the cases in which no operation was performed.

The bouillon filtrate was prepared for all cases in the following way: The respective strains of the organisms were allowed to incubate for two weeks and were then filtered through a Berkefeld filter. This was repeated by a second inoculation for the same period of time and a second filtration. A third inoculation of the filtered broth and incubation for seven days followed. All the strains were cultured separately in the course of the preparation of the bouillon filtrate. At the beginning of the work there were thirty-seven strains of staphylococci and

fourteen strains of streptococci, including Streptococcus viridans and Streptococcus haemolyticus. To this freshly prepared stock filtrate were added strains of streptococci obtained from the infected wounds of the patients under treatment.

RESULTS

CASE 1.—The patient sustained lacerations of the head when a bomb burst through the wall as he lay in bed. He remained unconscious for about two hours. A friend covered the bleeding wounds with dirty clothes. The next day the patient was taken to a hospital. He had a badly infected wound, which exposed the right parietal region of the brain through an opening 4 by 1.5 cm., and several infected lacerations of the scalp and face. For several days he was weak and unresponsive and had a high fever. There was an erythematous rash on the face. He was transferred to the Chinese Red Cross General Hospital on March 10. There was intermittent fever as high as 39.2 C. (102.7 F.) for about a week after admission. All the wounds were covered uniformly with a greenish-yellow exudate containing large numbers of gram-positive streptococci and diplococci. A culture taken on March 11 showed: Streptococcus haemolyticus, Streptococcus nonhaemolyticus (preponderance of growth), Staphylococcus aureus and Staphylococcus albus. The first treatment consisted of irrigation and dressings with surgical solution of chlorinated soda. There was no noticeable change in the appearance of the wounds, although as time went on the patient became responsive and cooperative and the fever disappeared. Bacterial filtrate was applied on the dressings used for the parietal wound as follows: On March 16 the filtrate was applied four times; at the end of the day the lower edge of the wound was pink; the rest was coated with purulent exudate. On March 17 the filtrate was applied three times; a band of pink granulation was seen at the lower part and along the upper edge of the wound. On March 18 the filtrate was applied once. Beginning on March 19, the filtrate was applied twice a day. The wound appeared clean except for a slender tongue of exudate. The parietal wound gradually became clean, and before the patient's discharge from the hospital it was completely covered by a growth from the surrounding scalp.

The smaller lacerations of the scalp were treated with irrigation and dressings with surgical solution of chlorinated soda until March 21. Although there was distinctly less purulent exudate from the wounds at the end of that time, they were still infected, and on March 21 treatment with the filtrate was applied for nine days, the dressings being changed only once a day. A burrowing gash on the right cheek failed to improve under dressings either of surgical solution of chlorinated soda or of filtrate, and on March 28 the wound was opened widely and was dressed with filtrate-soaked gauze. All the wounds of the head and face appeared clean by March 30 and proceeded to close in due time without further incident.

Summary.—A heavily infected parietal wound on the right side, which exposed the surface of the brain, showed little or no improvement under irrigation and dressings with surgical solution of chlorinated soda during two weeks of treatment. The first definite improvement appeared on the second day, and there was marked improvement on the fourth day, of treatment with filtrate. Improvement continued gradually until complete healing was effected. In the meantime small open lacerations of the scalp became clean under a combination of treatment with surgical solution of chlorinated soda and filtrate, but an infected burrow on the cheek resisted both types of therapy until it was widely opened surgically; it then healed promptly with the application of filtrate dressings.

CASE 2.—A tangential parieto-occipital wound on the left side was sustained early in February (the exact date is not known), which exposed the brain through an elliptic opening with a horizontal axis of 6 cm. and a vertical one of 3 cm. Initial unconsciousness, delirium and protracted delirioid behavior followed. Treatment was applied in the routine manner with irrigation and dressings with surgical solution of chlorinated soda, from the time of admission, on February 13, until March 11. In spite of this long period of treatment, the wound remained uniformly covered with a thick, dirty, grayish-yellow exudate. On March 9 a smear showed gram-positive and gram-negative diplococci and streptococci, gram-negative bacilli, polymorphonuclear cells and débris. A culture taken on the same date showed Staph. albus, Staph. citreus, and S. pyogenes, type 1. Dressings soaked in bacterial filtrate were then applied as follows: On March 11 a single application of filtrate was made late in the afternoon. On March 12 the filtrate was applied three times. On March 13 the filtrate was again applied three times; there was a slight subjective improvement. On March 14 the filtrate was applied twice; the upper part of the wound was free from exudate. On March 15 the filtrate was applied once, and, beginning on March 16, it was applied twice a day. On March 19 the exudate was limited to the lower edge of the wound and to a tongue that extended into the upper half. On March 22 the wound was almost entirely clean. A culture showed Bacillus cutis-communis and Bacillus pyocyaneus. A culture on March 24 showed Staph. albus, B. cutis-communis and B. pyocyaneus. The dressings with the bacterial filtrate were then discontinued, and dressings with surgical solution of chlorinated soda were resumed. In the course of a few days the wound began to be superficially clean for the first time, but evidence of a slight underlying residual infection remained, because the patient continued to have delirioid behavior. Soon afterward a transient phlebitis or lymphangitis of the neck developed. In spite of an apparently clean surface the wound failed to close during the rest of the patient's stay in the hospital. He was transferred elsewhere for further treatment.

Summary.—A badly infected tangential parieto-occipital wound on the left side, which exposed the surface of the brain, remained heavily coated with purulent exudate for a month under treatment with daily irrigation and dressings with surgical solution of chlorinated soda. On the third day of intensive treatment with filtrate there was a distinct improvement, which slowly continued until, on the eleventh day of therapy, the surface of the wound appeared clean. But the further course of the case indicated the existence of a residual underlying infection not completely cleared up while the patient remained in our care.

CASE 3.—On February 5 a tangential through-and-through bullet wound at the vertex of the skull drove fragments of bone into the underlying brain, for the most part just to the left of the midline. Paralysis of all four extremities followed, but this condition improved rapidly. A purulent discharge from the wound decreased but did not disappear under treatment with irrigation with surgical solution of chlorinated soda. Paralysis of the right arm and leg and of the left foot remained stationary after the end of February. Surgical treatment was postponed until malaria was brought under control by quinine. An operation on March 30 evacuated a small amount of purulent material and led to the removal of four small fragments of bone embedded in the brain. A culture on March 16 showed Staph. aureus (abundant growth), a gram-positive streptobacillus and B. pseudodiphtheriae (a few). Dressings soaked with filtrate were then applied as follows: On April 1 the filtrate was applied four times. On April 2 the filtrate was applied three times; there was a slight immediate improvement in the motility

of the legs, but sensory changes were more extensive and severe than before the operation. On April 3 and 4 the filtrate was applied twice. On April 5 the filtrate dressings were discontinued. The wound appeared clean. Dressings with surgical solution of chlorinated soda were then instituted and were continued until the wound closed without incident. Sensory disorders decreased rapidly until the middle of April, when they and the motor paresis proceeded *pari passu* to a slow but definite improvement up to the time of the patient's transfer elsewhere.

Summary.—Small bony fragments were driven into the brain by a tangential through-and-through bullet wound at the extreme vertex of the skull. There was an initial clinical improvement as the purulent exudate from the wounds decreased with irrigation with surgical solution of chlorinated soda. The course was then stationary until operative exposure and removal of the embedded bony fragments. Postoperative dressings with bacterial filtrate were applied for four days, after which time the wound appeared clean; dressings treated with the solution of chlorinated soda were then applied, and healing continued to closure without incident.

CASE 4.—The patient had received a penetrating wound in the right parietal region, caused by a bullet which was said to have been fired from a Japanese airplane. He had been admitted to a hospital elsewhere. The wound had closed promptly at the surface, but motor and sensory symptoms in the left arm and leg had increased. He was transferred to the Chinese Red Cross General Hospital on March 7. An operation performed on March 22 revealed an abscess of the brain, from which about 5 cc. of thick pus was evacuated. A culture of this material showed hemolytic and nonhemolytic streptococci. A cigaret drain soaked in bacterial filtrate was inserted, and the wound was closed around it. Dressings wet with filtrate were then applied as follows: On March 22 a cigaret drain and dressings soaked with filtrate were applied at the time of the operation. On March 23 the filtrate was applied three times. A drain moistened with filtrate was applied and was left in place. There was considerable pus. On March 24 the filtrate was applied twice; there was still considerable pus. From March 25 until April 5 the filtrate was applied once a day. On March 26 there was distinctly less pus on the dressings. By April 6 the purulent exudate had almost completely disappeared, and dressings with surgical solution of chlorinated soda were resumed. The first spontaneous movements of the left arm occurred on April 13. Improvement continued slowly, with complete closure of the wound, and the patient was eventually transferred elsewhere.

Summary.—A parietal bullet wound on the right side led to an abscess of the brain. After surgical exposure and drainage, the wound healed without incident under treatment with drains and dressings moistened with filtrate.

CASE 5.—A through-and-through bullet wound sustained on February 21 left one opening in the right parietal region and another in the left occipital region. There was a slight purulent discharge from both wounds, intermittent fever for about a week and delirioid behavior for a few weeks after admission. Both wounds were enlarged to allow better drainage and were then treated with daily irrigation and dressings with surgical solution of chlorinated soda. In spite of this treatment the purulent discharge increased in amount from both wounds, particularly from that in the parietal region, where the patient complained of increasingly severe pain. A culture taken on March 9 showed Staph. citreus and Staph. epidermidis-albus. Both wounds were again given wider surface exposure on March 12, and dressings wet with filtrate were applied as follows to the parietal wound: On March 12 the filtrate was applied once, at the time of the operation.

On March 13 and 14 it was applied three times. From March 15 to March 21 it was applied twice a day. The patient suffered less pain. On March 16 there was an increase of purulent exudate. Beginning on March 21, the filtrate was applied once a day. On March 23 the patient experienced dizziness, choked disks, slight ataxia on the left side and paresis of the left arm. On March 24 an operation revealed a deep abscess in the right parietal region, from which 3 to 4 cc. of thick pus was obtained and four or five fragments of loose bone were removed. A culture taken on March 24 showed nonhemolytic streptococci, Staph. epidermidis-albus and B. pyocyaneus. A cigaret drain was inserted, wet with filtrate, and the . wound was covered with gauze moistened with the filtrate. After the operation the parietal wound was treated daily with filtrate dressings as before. For a while the weakness and incoordination on the left side were worse than before, but pain decreased, and the choked disks promptly improved. The wound soon became clean and healed slowly without further incident.

Until the first of April the surface of the occipital wound had appeared relatively clean and was treated with daily dressings with surgical solution of chlorinated soda. But beginning on April 1 an increasing amount of purulent discharge came from it each day. On April 14 a wide incision was made in the occipital part of the scalp; about 15 cc. of pus was evacuated from the scalp and about 2 cc. was evacuated from a small underlying abscess of the brain. Bacterial filtrate was then applied for the first time by means of the dressings used for the occipital wound, according to the following schedule: On April 14 the filtrate was applied four times; on April 15 it was applied three times; beginning on April 16, it was applied twice a day. On April 16 herniation of the brain began to develop through the occipital bony opening. For the next ten days, the condition remained unchanged. The herniating mass was surrounded by pus which exuded from under the edges of the bone. Dressings with surgical solution of chlorinated soda were resumed in place of those with the filtrate. On April 27 the herniating mass was cut away and the base of the wound was sealed by the use of high frequency current. Another herniating mass developed, but the wound remained cleaner on the surface than before. On May 21 the mass was treated with. 156 mg.-hrs. of radium; the hernia receded at once, leaving a clean granulating wound by the end of May.

Summary.—A through-and-through bullet wound became infected at the points of entrance and exit, in the right parietal and left occipital regions. Superficial exposure of the wounds, followed by irrigations and dressings with surgical solution of chlorinated soda, failed to cure the infection within three weeks. Further superficial exposure and treatment of the parietal wound with filtrate for eleven days failed to bring improvement. An operation revealed a deep abscess of the brain in the right parietal region. After evacuation of the abscess and drainage and dressings with the filtrate, the wound proceeded to heal without further incident. Then purulent exudate increased in the occipital wound. An operation evacuated considerable pus from the scalp and revealed a small abscess of the brain. A hernia of the brain immediately appeared, with pus exuding in small amounts from under the bone. Neither treatment with filtrate nor irrigation with surgical solution of chlorinated soda brought immediate improvement. Three weeks after the appearance of the hernia the occipital wound also appeared clean and the hernia receded.

CASE 6.—A wound of the left frontal region, exposing the brain, had become infected. Removal of fragments of bone, drainage and irrigation and dressings with surgical solution of chlorinated soda and with saline solution had been

carried out elsewhere. The patient was transferred to the Chinese Red Cross General Hospital on March 18, with an infected, bloody mass protruding slightly through the opening in the frontal bone. A smear showed gram-positive streptococci, diplococci and some staphylococci. Cultures taken on March 18 and 19 showed Str. haemolyticus, Staph. albus and Sarcina subflava. The patient was stuporous, febrile and toxic; there were harsh bronchovesicular breath sounds and tachypnea. Dressings soaked with filtrate were applied as follows: On March 18 the filtrate was applied once, in the evening. On March 19 the filtrate was applied three times. A lumbar puncture revealed 2,650 cells; reducing substances, 29.4, and chlorides, 676. The spinal fluid gave a positive reaction for globulin; the Wassermann reaction was negative. A culture showed no growth. On March 20 and 21 filtrate was applied twice a day, and, beginning on March 22, it was applied once a day. Soon after admission the patient grew profoundly stuporous and definite signs of meningitis developed. Repeated lumbar punctures yielded results similar to the first. A positive culture of Str. haemolyticus was later obtained from the spinal fluid, but a blood culture showed no growth. The patient died on March 28.

Summary.—An infected frontal wound on the left side, exposing the brain, showed no improvement following the application of filtrate in a patient with toxemia from a disseminated infection. Death occurred eight days after admission.

Case 7.—A tangential wound at the extreme vertex of the skull drove fragments of bone into the brain. The patient had had first aid treatment and dressings before he was transferred to the Chinese Red Cross General Hospital on March 16. On admission he was quiet, and the wound allowed good contact, but a large infected fungating mass protruded from the opening in the skull. Cultures taken on March 18 and 19 showed Staph. aureus and Micrococcus gingivalis; a few colonies of nonhemolytic streptococci were recovered on the following day. The initial dressings with surgical solution of chlorinated soda were changed for surface dressings with filtrate, but after a few days it was obvious that the filtrate did not reach the underlying seat of the infection. On March 23 the herniating mass was destroyed by fulguration and filtrate dressings were continued. Another mass with its attendant purulent coating pushed out through the bony opening. Dressings with the filtrate were discontinued after a few more days, and irrigation and dressings with surgical solution of chlorinated soda were instituted. Various measures, surgical and physiologic, were applied through dehydration, but the fungating mass continued to develop. The patient grew stuporous and died on April 8. Autopsy showed bony fragments embedded deep in the upper left parietal region and a wide zone containing inflammatory and hemorrhagic plaques in the upper half of both hemispheres, particularly on the left side and around the left lateral ventricle.

Summary.—A tangential wound at the vertex of the skull drove fragments of bone into the brain. The patient was transferred to the Chinese Red Cross General Hospital with an infected hernia of the brain. There was no improvement under superficial treatment with filtrate. The patient became stuporous and died. Autopsy showed widespread inflammation in the brain around the wound and in the left lateral ventricle.

Case 8.—The patient sustained a through-and-through bullet wound from the left temporal to the left frontal region, just above the orbit of the eye, on April 8. At operation, on April 12, an apparently clean field was opened, with considerable attendant bleeding. The track of the bullet was exposed; in only one place, the size of a pea, was the meningeal covering of the frontal pole torn through by

the bullet. A few bony fragments outside the meninges were removed. A culture taken from the field at the time of operation showed no growth. Treatment by packing with gauze to control bleeding and by applying dressings soaked with filtrate was instituted. Postoperative dressings with filtrate were applied four times on April 13, three times on April 14 and twice a day from April 15 to May 3. On April 16 there was a seropurulent discharge from the frontal wound. On April 19 sanguinopurulent material gushed from the temporal wound when the packing was removed. On April 21 there was a thick purulent discharge from both wounds and frontal irrigation came from the nose. At this time a culture showed a heavy growth of Str. haemolyticus and Staph. aureus. On May 3 a second operation was performed; the field was reexposed and better drainage was provided. The wound closed without further incident under treatment with daily dressings with surgical solution of chlorinated soda.

Summary.—Four days after a through-and-through bullet wound extending from the left temporal to the left frontal region was sustained, an operation exposed the track of the bullet. Treatment with prophylactic drains and dressings soaked in filtrate was followed by the appearance of a heavy infection, which did not clear up until a second operation gave still wider exposure and treatment with dressings with surgical solution of chlorinated soda was instituted.

<center>COMMENT</center>

The cases reported here are too few to warrant a final decision as to the value of bacterial filtrates in the treatment of infected wounds of the brain. Yet from these few observations some points stand out as leads for further investigation.

In the first place, the frequent application of bacterial filtrates to fully exposed wounds of the brain or to meninges with surface infection may prove to be very effective. In the series presented, only the first two cases fall in this category. The improvement in the appearance of the wounds, which were both infected predominantly with hemolytic streptococci, was striking after treatment with filtrates began to be intensively applied. Emphasis is laid on three points which appear to be requisite for success with this type of treatment: 1. Exposure must be complete so that the whole infected surface is brought in contact with the dressings. 2. The dressings should be moistened with the filtrate at frequent intervals. 3. The infection must be focal and limited to the surface of the wound. The first case reported gives an illustration of the necessity of observing these points. The parietal wound which exposed the brain was heavily infected but was wide open, and the infection was superficial. This was the first wound to become clean under treatment with filtrates. The superficial lacerations of the scalp, to which filtrates were applied later and less often, cleared up next. But the burrowing gash on the face resisted applications of both surgical solution of chlorinated soda and filtrate until it was opened widely with the knife and dressed with gauze soaked in filtrate. In the second case there was a widely exposed wound in which the infec-

tion seemed to be limited to the surface. With intensive use of filtrates the change in the appearance of the wound was quite as definite as in the first case, for the superficial infection cleared up rapidly under this treatment, but the final result was not so good, a fact which is attributed to the likelihood of a slight but persistent infectious process in the underlying tissues.

A second feature in this series of observations is the length of time before results became apparent. In several of these cases treatment with bouillon filtrate was continued for from one to three weeks. In only two cases can any success be claimed with this treatment (cases 1 and 2). In both these cases treatment with prolonged irrigation and dressings with surgical solution of chlorinated soda led to little or no change, but within four days after intensive use of filtrates was begun a pronounced improvement took place. The suggestion is accordingly made that bacterial filtrates are indicated in all cases of open wounds exposing the meninges or brain which appear superficially infected with streptococci or staphylococci, and that improvement in the appearance of the wound will be definite within four days, if at all. If no improvement has taken place after four days of intensive trial of the treatment with filtrates one must consider the likelihood of an extension of the infection beyond the surface of the wound, e. g., focal or diffuse encephalitis, abscess of the brain, ventriculitis, meningitis or a pus pocket under the scalp. As examples, in case 5 of this report there were abscesses of the brain; in case 6, encephalitis and meningitis, and in case 7, encephalitis and ventriculitis.

In two cases in this series (3 and 4), a recognized abscess or focal encephalitis developed at the site of the wound before treatment with filtrates was considered. The areas were opened at operation, and drains, packing and dressings were applied as usual, except that they were moistened with filtrate instead of with surgical solution of chlorinated soda or some other bactericidal solution. Also, with the parietal abscess in case 5, postoperative dressings were wet with filtrate. In all three cases the healing of the wounds took place satisfactorily. No statement can be made from these cases alone, however, as to the relative merits of using filtrates or other applications on drains or dressings after operation for the abscesses of the brain. For in regard to effectiveness and to the rate of closure of infected wounds lying deeper in the brain tissue we could see no difference between the results obtained with surgical solution of chlorinated soda and those obtained with Bezredka's filtrates on the postoperative dressings. But we are inclined to lay aside, at least for the time being, the use of bacterial filtrates in the treatment of abscesses of the brain. We see no special advantage in their use in such cases, and there are distinct theoretical difficulties in establishing contact between the whole infected

area and the drains, as well as in maintaining sufficient concentration of the filtrate to be effective inside the abscesses.

Finally, the action of the filtrates could be that of a bacteriophage. The therapy was successful only on production of conditions which were favorable to that action: infection with the streptococcus and staphylococcus already present, polyvalent streptococcus-staphylococcus filtrate, an open wound to provide good contact and frequent moistening of the dressings to give the necessary concentration of filtrate. The other objective which was suggested during the work with the filtrates was the establishing of local immunity in the tissues surrounding the infection. But so far we have no clinical proof that such an action is possible in the brain and meninges, and there is some evidence against it. The patient in case 8 came to us soon after his injury. The track of the bullet appeared to be clean at the time of the first operation, and a culture showed no growth. But the application of bacterial filtrate for the sake of providing local immunity as a prophylactic measure against infection was soon followed by a severe infection with Str. haemolyticus and Staph. aureus. Furthermore, unpublished experiments performed on rabbits, while not conclusive, gave no positive indication that local immunity can be developed in brain tissue by saturating it with Bezredka's streptococcus filtrates.

Thus the clinical results obtained by us in treating infected wounds of the brain with bacterial filtrates, the proposed indications for its use and the theory of bacteriophage action all fall in line. Theoretically this therapy should work with rapidity when the proper filtrate is brought in good contact with bacterial growth in sufficient concentration to cause lysis of the organisms; practically the results seem to become apparent within about four days or less in cases with surface infection of thoroughly exposed wounds when the dressings are repeatedly moistened with the proper filtrate. Failure to obtain improvement within four days may be taken as an indication of improper contact or of insufficient concentration, that is, of a poorly matched filtrate, inadequate exposure of the wound, a deep or disseminated infection or some other clinical complication.

SUMMARY

1. Two patients with severely infected wounds on the surface of the brain showed marked improvement within four days following frequent applications of a polyvalent streptococcus-staphylococcus filtrate to the dressings. Prior to treatment with the filtrate they had shown no improvement with irrigation and dressings with surgical solution of chlorinated soda.

2. Three patients with infected wounds of the brain showed no improvement after more than four days' trial of treatment with filtrates. These patients later proved to have a deep or disseminated infection of the central nervous system.

3. It is suggested that the successful results were due to bacteriophage action, which requires good contact of the filtrate in sufficient concentration to cause lysis of the bacterial organisms. The treatment indicated is frequent moistening of the dressings with the proper filtrate. The clinical indications for this treatment are a wide exposure of the wound and a surface infection of the brain or meninges. Improvement should begin within four days if this type of treatment is to be adequate.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

E. STARR JUDD, M.D.
ROCHESTER, MINN.

LINWOOD D. KEYSER, M.D.
ROANOKE, VA.

JEAN VERBRUGGE, M.D.
ANTWERP, BELGIUM

ADOLPH A. KUTZMANN, M.D.
LOS ANGELES

ALEXANDER B. HEPLER, M.D.
SEATTLE

AND

ROBERT GUTIERREZ, M.D.
NEW YORK

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URETER

Transplantation.—Ormond [28] reported that the rectum and lower part of the sigmoid flexure are the customary sites for ureteral transplants, and although the content of these segments constitutes a definite objection, and renal infections do occur, the functional results are reasonably good. Occasionally technical obstacles to the use of the sigmoid flexure or rectum are encountered, making it necessary to use a higher part of the bowel, and in a number of such instances the right ureter has been implanted into the cecum.

A series of experiments on animals was carried out. The procedure in all cases was the same: first, implantation of the right ureter into the cecum, following Coffey's technic as nearly as possible; second, about ten days later, removal of the left kidney. The animals all recovered rapidly from the first operation, and after the first day were as active as before. At first, after the second operation, there seemed to be no change, but gradually they became less active, and finally went into a semistuporous condition. At death, the value for nonprotein nitrogen of the blood was much elevated.

Ormond's interpretation of these findings, taken in conjunction with other experimental work, is that urine, emptying into the cecum,

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28. Ormond, J. K.: Some Experimental Work on the Site for Ureteral Transplant, J. Urol. **29**:15 (Jan.) 1933.

is reabsorbed, at least in great part, and entering the blood stream is again passed through the kidneys, again excreted and reabsorbed, and so on. Consequently, the products that normally are removed by the kidneys accumulate in the blood until uremia and death occur. Moreover, the kidneys themselves are injured by the strain thrown on them by perfusion with blood that is overlooked with urinary constituents. His conclusion is that transplantation of the right ureter into the cecum is at best a useless procedure, and may be harmful, as is suggested by the occasional presence of injury to the mucosa at the point of entrance of the ureter.

Quénu and Fey[29] stated that on two occasions they had cut a ureter accidentally, following which they performed ureterocystoneostomy; in both cases repair was made immediately, and the patients were cured without a fistula. The second case, controlled urologically two years later, presented certain points of considerable interest. In this case, the ureterocystoneostomy was performed only a few moments after the ureter had been cut, during an operation for removal of a large fibroma. The paramount consideration here was the conservation of a sound kidney with normal secretion. Every ureterocystoneostomy which does not achieve this end should be regarded as a failure. For the success of such an operation it must be determined that the kidney conserved functions normally. Neither clinical nor cystoscopic proof alone is sufficient to show that this object has been attained, for clinical healing may coincide with the death of a kidney. A number of experiments, operative findings and postmortem examinations have shown that a ureter may contract and even become obliterated, and a kidney may undergo dilatation and atrophy, without any symptoms. For this reason, 30 or more cases reported in the literature are useless scientifically, since they bring no other proof of cure. Only 1 of the 50 cases reported can meet the criterion of functional examination after bilateral catheterization, which makes it possible to judge of renal function by the quantity and quality of the urine secreted in a given time. This may be due in part to the site of the neostomy, the surgeon having, for his own convenience, made an implantation into the dome of the bladder too high to permit catheterization.

Although the authors' case has not yet stood the test of time, they regard the result obtained as astonishingly good, because, first, the patient feels well; second, the orifice of the neostomy, permeable to the catheter, is neither obliterated nor contracted; third, vesicorenal reflux is prevented; fourth, neither the ureter nor the pelvis is dilated; fifth, the

29. Quénu, Jean, and Fey, Bernard: Résultat éloigné d'une urétéro-cysto-néostomié, Bull. et mém. Soc. nat. de chir. **58**:1377 (Nov. 16) 1932.

urine collected in the pelvis is uninfected, and sixth, the kidney secretes a normal quantity of urine containing urea and sodium chloride in a concentration greater than on the opposite side. In addition to the usual functional tests, they also have examined the patient cytobiologically and cystographically, and by intravenous pyelography. Absence of reflux, of reno-ureteral dilatation and of infection suggests a good prognosis.

Without being fully able to account for their good result, the authors ventured to state that the following procedures may have played a part: first, the immediate implantation of a freshly cut ureter in a case in which the kidney was neither dilated nor infected; second, selection of the site of implantation as near as possible to the normal ureteral orifice; third, the use of the Payne procedure of implantation, with two sutures at a distance from the orifice, and fourth, decision not to introduce a catheter either during or after operation.

[COMPILERS' NOTE.—The problem of reimplantation of the ureter into the bladder after any surgical injury during operation has attracted considerable attention for many years, but in reality the value of this procedure has never been actually tested until cystography and, more properly, intravenous urography came into use, by which the condition of the kidney could be tested functionally. It has been the general belief that the kidney ultimately was destroyed by the vesico-ureterorenal reflux which, in turn, was caused by lack of sphincteric action at the newly formed ureteral orifice; also, by the tension of the ureter which distorted the bladder and interfered with the dynamic contractions of the ureter and the emptying time of the renal pelvis. However, Quénu and Fey apparently have satisfied the requirements, although sufficient time has not as yet elapsed to prove the final outcome, for not infrequently urinary infection, pyelonephritis, hydro-ureter and hydronephrosis ultimately develop, and these may eventually call for ureteronephrectomy.]

Beer,[30] in a recent communication read before the New York Academy of Medicine, reviewed his results in a group of 41 cases in which ureterocystoneostomy had been performed, as determined by intravenous urography, although in many of the cases cystography revealed the presence of vesicorenal reflux, and in some of them catheterization of the ureters has never been possible. It can be concluded, therefore, that although ureterocystoneostomy should be performed in an attempt to save the kidney whenever the ureter has been injured, the patient should be informed of the possibilities of a surgical lesion developing at a future time.

30. Beer, Edwin: Value of Ureteral Re-Implantation in the Bladder, Am. J. Surg. **20**:8 (April) 1933.

Obstruction.—Ockerblad[31] reported 27 cases of noncalculous, acute ureteral obstruction. The oldest patient was 68 years of age and the youngest, 2 years. Fourteen patients were females and 13 were males. In all of them, pain was the predominant symptom, varying slightly in degree. In each case there was an elevation of temperature, ranging from 100 to 105 F. In 19 there was a chill. In 22 of the cases nausea or vomiting, or both, occurred. In 4 cases the urine in the kidney was bloody when withdrawn by catheter. In every case the urine was under pressure. The amount withdrawn varied from 20 to 500 cc. Invariably some pus was present in the urine from the obstructed kidney. In every case relief from pain was immediate on ureteral catheterization.

The various etiologic factors presented an interesting study. In 11 cases the cause of obstruction was unknown. Of the remaining 16 cases, 1 was definitely an instance of the wandering kidney described by Dietl. In 1 case a congenitally solitary kidney was blocked by seminal vesiculitis. One patient was a pregnant woman, in the fifth month of gestation. In another case, that of an infant, the condition was the result of congenital stricture of the ureter. In 1 case both ureters were tied at operation. In 1 case an appendical abscess was present; an aberrant blood vessel to the lower pole interfered with the ureter in 1 case; in 2 cases there were tuberculous strictures of the ureter; operative scars closed the intramural portion of the ureter in 2 cases; in 3 cases strictures closed the ureteral os, and large prostatic lobes growing upward under the mucosa impinged on the ureter in 2 cases. It is interesting that there were 5 congenital anomalies. There were no deaths from the disease. The two outstanding points in the diagnosis are the pain and the finding of urine under pressure.

Woytek[32] stated that "pseudonephrolithiasis" is the term applied by Allemann to that condition in which the symptoms are caused by organic inflammatory kinks and strictures in the upper part of the ureter, causing disturbances in function. These cases simulate closely cases of true stone, since colic and microscopic hematuria are often present. The cause is usually an inflammatory process of the perirenal tissue or of the kidney itself. Movable kidneys are associated with only a small number of cases. Woytek has seen 60 such cases since 1924 and has divided them into 2 groups: first, the cases with sudden onset, and second, those with gradual onset. Cases of the first group simulate cases of colic caused by stone; nearly always microscopic examination reveals blood in the urine along with the colic.

The author expressed the belief that some physicians do not accurately study their cases and consequently report large numbers in

31. Ockerblad, N. F.: Acute Ureteral Obstruction, J. Urol. **29**:32 (Jan.) 1933.
32. Woytek, G.: Ueber "Pseudonephrolithiasis," Beitr. z. klin. Chir. **156**:389, 1932.

which ureteral strictures were found. On the other hand, at the Mayo Clinic, where the cases are well studied, only 6 cases in which definite strictures were encountered were found in the course of 6,000 cysto-scopic examinations. In further studies made elsewhere (Braasch, Kenneth Frater) 2 cases of stricture were found in 93 cases. Schreiber found stricture in 13 per cent, whereas Campbell, in 13,000 postmortem examinations, observed stricture in only 1 per cent.

Woytek suggested that infection carried from foci by the blood stream often causes ureteral stricture (tonsillitis, influenza, scarlet fever, diphtheria, puerperal sepsis, otitis media, infections of teeth, enteritis, salpingitis, prostatitis and seminal vesiculitis). The characteristic findings seem to be infiltration of the mucosa and musculature with round cells.

Absolute proof of ureteral stricture or kink is best given by retro-grade ureteropyelograms. Intravenous urography can be of secondary help.

Treatment is chiefly conservative. In cases in which there is irreparable injury to the ureters it may be necessary to perform nephrectomy.

Granuloma.—Hamer, Mertz and Wishard [33] stated that granulomas of the ureter do not give rise to pathognomonic symptoms. Hematuria, usually recurrent and gross, is the chief complaint. The passage of large clots may cause colicky pain. Positive physical findings depend on the presence of obstruction and on loss of blood and infection; they are not pathognomonic. They stated that the gross appearance of a ureteral granuloma varies according to the extent of the lesion. There may be thickening of the ureteral wall, with increased vascularity and evidence of a periureteral inflammatory reaction. In the event of an extensive local lesion, a distinct tumor may be palpated in the ureter. On section, the ureteral mucosa is found paved with reddish-purplish granulation tissue which bleeds easily when traumatized. If there is sufficient proliferation, polypoid masses may be present. There may be single or multiple areas, which may become confluent and may involve a considerable extent of ureter.

The authors expressed the belief that the most significant special urologic finding is in the pyelo-ureterogram, and indeed one cannot allow anything pathognomonic in its interpretation. The point of error lies in suspecting a true neoplasm. Obviously, the urographic findings must be protean, depending not only on the extent of surface involved, but also on the degree of proliferation and consequent type of filling defect observed. Single or multiple circumscribed filling defects,

33. Hamer, H. G.; Mertz, H. O., and Wishard, W. N., Jr.: Ureteral Granu-loma, J. Urol. 29:43 (Jan.) 1933.

together with a possible ragged appearance of the ureteral edges, may suggest neoplasm, granuloma or possibly tuberculosis.

Hamer, Mertz and Wishard suggested that without any means of establishing a definite diagnosis, treatment is obviously going to tend toward open operation, unfortunate as this may be in the presence of granuloma. When one has reasonable doubt as to the presence of a neoplasm, one may resort to ureteral dilation and medication directed toward the clearing up of both local infection and distant foci, but one dare not persist too long, unless improvement appears, lest the opportune time for removal of a true neoplasm be lost. On the other hand, hemorrhage may be so severe as to endanger the patient's life unless immediate operation is done. In conclusion, the authors stated that in view of the possibility of bilateral involvement, nephro-ureterectomy is warranted only in an emergency.

Nerve Supply.—Wharton [34] stated that the ureter receives a nerve supply which is independent of the innervation of the kidney and bladder. The nerves go directly to the ureter from the lowest renal ganglion, at the upper end of the spermatic plexus and from the abominal sympathetic nerves. Their dissection disclosed that there is a connection between the ureteral innervation and the plexuses that supply the ovary, testis and parietal peritoneum.

Wharton said that from the physiologic point of view, his clinical observations would lead him to conclude that cutting these ureteral nerves, as in ureteral denervation, does not interfere with the motor function of the ureter and does not cause atony, hydro-ureter, stricture or any ureteral disturbance. On the basis of clinical observations, he is of the opinion that one of the functions of these ureteral nerves is the transmission of painful sensations.

PROSTATE GLAND

Prostatectomy.—Illyes [35] used a tampon for hemostasis in suprapubic prostatectomy. After the arterial bleeding has been controlled, the assistant inserts a finger into the rectum to hold up the prostatic cavity, following which the tampon is packed carefully and evenly throughout the entire cavity. The tampon is left in for five days, during which the cavity is washed out alternately with ice cold water and with very warm water if bleeding occurs. Illyes has had practically no bleeding following this technic and is well satisfied with it.

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34. Wharton, L. R.: The Innervation of the Ureter, with Respect to Denervation, J. Urol. **28**:639 (Dec.) 1932.

35. Illyes, G. V.: Ueber die Tamponade nach Prostatektomie, Ztschr. f. urol. Chir. **36**:183, 1933.

[COMPILERS' NOTE.—Packing of the prostatic cavity with gauze has been employed extensively at various times in this country. Many surgeons still do this, claiming good results, and prefer it to the use of various types of hemostatic bags. The Hagner and Pilcher bags, and other modifications, are used in place of gauze in most clinics at the present time. They are simpler to use and efficient, cause little pain, and can be removed without causing secondary bleeding. Little is now written in this country concerning tampons and bags, for the descriptions of the newer operation of prostatic excision has practically displaced articles on prostatectomy.]

Transurethral Resection.—Bumpus [36] has reviewed 102 cases of urinary obstruction due to benign enlargement of the prostate gland in which he performed the transurethral operation, from 1925 to 1927. He chose this period for two reasons: first, because it gave a period of five years since the last operation, and second, because he had operated in more than 100 cases in the preceding years and felt that any failure that might be disclosed would not be ascribed to inexperience but to the procedure. In half of these cases Bumpus used the Caulk cautery punch, and in the other half, a modification of Braasch's cystoscope. The amount of residual urine prior to operation in the 102 cases varied from none to a large quantity resulting from complete retention; in 22 cases, the quantity was in excess of 200 cc. Fifty-seven patients were free from residual urine at the time of dismissal, and 15 others had less than 30 cc., making a total of 72 whose immediate postoperative result indicated success for the future.

After a survey of the 102 cases, five or more years after operation, Bumpus reported that 8 of the patients were dead. During the five years following operation in this series, transurethral resection was performed in approximately 300 cases, and 4 deaths occurred; none of these deaths was directly or indirectly attributable to bleeding, but was the result of infection following failure to remove sufficient tissue and completely eliminate residual urine. More than 100 patients had been operated on successfully since the last death. Records to date were available of 66 of the 102 patients. Adenofibromatous tissue was removed from 24 of them, of whom 18, or three fourths, had written that they were satisfied with the final results. Of 6 dissatisfied patients, 3 underwent prostatectomy, one a year later, another two years later and a third four years later.

Bumpus stated that records are available to date on 42 of 67 cases in which transurethral resection was done for inflammatory changes

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36. Bumpus, H. C., Jr.: Results Five Years After Transurethral Treatment of Benign Prostatic Obstruction, J. Urol. **28**:564 (Nov.) 1932.

in the prostate gland. Thirty of the patients have expressed satisfaction with the final results, whereas 12 are definitely disappointed.

Bumpus stated that this study of 102 cases in which prostatic tissue was removed through the urethra more than five years before, because of urinary obstruction, would indicate that with the improvement in technic which has occurred in the last five years, transurethral resection should be performed with less risk, with less time spent in the hospital and consequently with less expenditure of funds, and that the final functional result would equal in permanence that usually obtained after prostatectomy.

In a study of 250 cases in which transurethral resection was done in the last seven years, Bumpus [37] found that in 204 cases (81.6 per cent) 5 Gm. of tissue or less was removed. If it is estimated that two fifths of the hypertrophic tissue removed at prostatectomy represents the amount that is actually obstructing the urethra, one may consider any prostate gland the hypertrophic portion of which weighs less than 50 Gm. as suitable for transurethral resection. In but 32 per cent of 575 cases in which prostatectomy was performed at the Mayo Clinic in the last three years did the removed tissue weigh more than 50 Gm. But included in this 32 per cent are many cases in which the patients had complete retention, extensive renal impairment and often grave cardiac injury, not to mention extreme senility in some cases, when they were first seen. Such patients require suprapubic drainage at the earliest moment consistent with safety, and, needless to add, relief of the obstruction should be undertaken with the minimum of risk. The institution of suprapubic drainage greatly extends the applicability of transurethral resection for reasons already stated. As a result, at the clinic it was found possible to relieve patients of their suprapubic drains in cases in which the risks had seemed too great to warrant prostatectomy.

Up to January, 1932, Bumpus had removed the obstructing portion of the prostate gland in 44 cases in which cystostomy had been performed previously. In 19 of these, the cystostomy had been done as the first stage of prostatectomy in two stages, but the decrease in the size of the gland after drainage, or more frequently the poor physical condition of the patient, made the transurethral method of removal seem preferable.

Among the 44 patients were 3 with carcinoma of the prostate gland who previously had undergone suprapubic drainage and, becoming dissatisfied with the arrangement, demanded relief. One of these patients, aged 73, died of embolic pneumonia. In the remaining 72 cases in which cystostomy had been performed, the transurethral method of treatment

37. Bumpus, H. C., Jr.: Prostatic Obstruction Relieved by Suprapubic Drainage Followed by Transurethral Resection, Tr. Am. A. Genito-Urin. Surgeons **25:** 211, 1932.

was used because the urinary obstruction was not great. In 12 of these 22 cases, recent resection of a diverticulum made another major operation a thing to be avoided, and in the remaining 10, removal of stones from the bladder had resulted in so much diminution in the size of the prostate gland that prostatectomy hardly seemed justified for removal of so comparatively small an amount of tissue. Letters were received from 38 of the patients who accepted transurethral resection after previous cystostomy. Twenty-nine expressed themselves as satisfied with the results, whereas 9 were disappointed.

Bumpus concluded that although transurethral removal of obstructing prostatic tissue had been made possible by electrocoagulation, the applicability of transurethral resection has been extended by the performance of suprapubic cystostomy prior to resection. Suprapubic cystostomy is especially useful in operating on patients who are suffering some serious impairment of parenchymatous organs.

Crowell and Davis [38] attempted to analyze clinically, by questionnaire and by personal examination, results in 385 cases in which transurethral resection had been carried out according to their plan in the last five years. Two hundred ninety-nine patients returned the answered questionnaire, and 49 reported for examination. One hundred and seven patients had not returned definite replies to the questionnaire.

The authors found that the clinical results obtained were better in cases in which operation had been performed more than six months before the questionnaire was answered. There is nearly always some tenderness, accompanied by tenesmus, during and following urination for several months after the operation, but this finally subsides. They presumed that with time the remaining portion of the gland becomes atrophied and retracts so as to enlarge the vesical opening and enable the patient to empty the bladder without difficulty. A number of the patients were subjected to cystoscopy from one to five years after operation, and the prostatic urethra was found unobstructed by the remaining portion of the gland.

In the analysis of questionnaires and reexaminations, it appeared that 247 patients had no difficulty in emptying the bladder, while 16 did have difficulty. Of these patients, 110 emptied the bladder once at night; 77, two or three times, and 59 not at all. Three had incontinence, and 5 noted leakage at times when the bladder was full. Ninety-three had gained weight, and 133 had not changed in weight.

Day [39] considered an initial series of 71 cases in which loop resection was performed by seven different urologists. Fifty-three oper-

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38. Crowell, A. J., and Davis, T. M.: Results in 385 Cases of Prostatic Resection by the Davis Method, Tr. Am. A. Genito-Urin. Surgeons **25**:215, 1932.

39. Day, Robert: Endoscopic Resection of the Prostate, J. Urol. **28**:569 (Nov.) 1932.

ations were performed on clinical patients, all in the same hospital, and 18 were on private patients. Eleven resections were performed by the same attending urologist in his clinical service; 21 were about evenly divided among five other urologists in the service, and the remainder were performed by Day himself. There were 9 deaths, 6 from primary hemorrhage and ensuing shock, 2 from multiple abscesses of the kidney and 1 from acute dilatation of the heart. The mortality rate for the entire series was 12.7 per cent. The first 41 patients of the series were unselected. In size, most of the prostate glands were graded 4. All of the deaths were among these first 41 patients, a mortality rate of 22 per cent. A considerable percentage of these 41 patients had been considered either completely unfit for prostatectomy or as extremely bad risks. The remaining 30 were selected, 18 of whom were private patients; none of these 30 patients died. The most frequent cause of death was primary hemorrhage with ensuing shock. In the later series of selected cases the freedom from undue bleeding was attributed, for the most part, .to the employment of a two-machine hook-up. Day stated that in his total personal series of 39 cases in which major loop resection was performed, there were 2 deaths. Four of the 71 patients in the series were later subjected to prostatectomy.

Malignancy.—Smith [40] summarized the effect of radium applied to the prostate gland in 31 operations on 29 patients. There were 6 deaths from operation, 3 of which were due to pulmonary emboli. Nine other patients died of carcinoma within one year. The average length of life of those patients who survived operation but who died of carcinoma was thirteen and a half months. Seven of the patients were still alive when the report was written, 4 patients less than one year, 1 thirteen months, 1 eighteen months and 1 four years after operation.

Smith said that in 3 cases it was demonstrated that carcinomatous cells had survived extensive irradiation (from 3,800 to 5,000 millicurie hours). Since it is not feasible to destroy the entire prostate gland by massive, destructive radiation, the object of treatment by radium should be to employ a dose insufficient to cause extensive necrosis, with a view to causing fibrosis and a decrease in the malignancy of the tumor.

Brandesky [41] found 154 cases of sarcoma of the prostate gland in a review of the literature, and added a case of his own. Sarcoma of the prostate gland is rare, usually afflicting young subjects. In the reported cases, 31 per cent of the patients were in the first decade of life; 17 per cent had passed the age of 50. The prognosis is always unfavorable.

40. Smith, G. G.: What Does Radium Do to the Malignant Prostate? Tr. Am. A. Genito-Urin. Surgeons **25**:155, 1932.

41. Brandesky, Walter: Primäre Prostatasarkome, Wien. med. Wchnschr. **82**:182, 1932; abstr., Am. J. Cancer **16**:1183, 1932.

Brandesky's patient was a man, aged 56 years, who had urinary obstruction. Cystotomy was done, following which the patient had repeated attacks of burning pain and tenesmus. Rectal palpation revealed a large, soft, fluctuating prostate gland protruding into the rectum. Three months after cystotomy the tumor was partially removed. It was adherent to the rectum and grossly was of papillary structure. Microscopic examination revealed a necrotic, spindle cell sarcoma. The patient died shortly afterward, and at necropsy the diagnosis of sarcoma of the prostate gland was confirmed.

BLADDER

Tumors.—Müller [42] reported on conditions of the urinary bladder in workers in aniline dyes at Basel. There were 4 cases of acute hemorrhagic cystitis, 1 case of chronic ulcerative cystitis, 19 papillomas of which 6 later became malignant and 36 definite carcinomas. The time in which the worker had been handling different chemicals varied from two to thirty-six years, averaging seventeen years and four months. For the 9 benign tumors, the average was fourteen years, and for carcinoma, nineteen years.

In contrast to the observation of Simon, who found a fairly low degree of malignancy in aniline carcinomas, the growths at Basel were highly malignant and rarely operable, and readily formed metastatic growths. The papillomas in Müller's cases were treated satisfactorily by endovesical fulguration. In 5 cases of carcinoma in which the tumor was in a satisfactory area resection of the bladder was done. Of these patients, 2 were well and working eight years after operation. In cases in which the tumor was on the side wall and base of the bladder, cystectomy was done, the ureters being transplanted into the intestine.

A rigid system of examination and prophylaxis is being carried out among the chemical workers in Basel. The urine is examined at regular intervals, and any patients who have suggestive symptoms are examined cystoscopically.

Redi and Marri [43] stated that the indications for extensive operation in cases of malignant tumor of the bladder are drawn chiefly from the size of the tumor, its base of implantation, its extent in surface and depth, the presence of metastasis and the general condition of the patient. Although total cystectomy is the operation of choice when the growth is extensive, in most cases the situation of the tumor and its infiltration into the wall of the bladder indicate partial cystectomy; this

42. Müller, Achilles: Ueber Blasenveränderungen durch Amine, Ztschr. f. urol. Chir. **36**:202 (Jan.) 1933.

43. Redi, Rodolfo and Marri, Piero: Sulla resezione parziale della vescica urinaria per cancro infiltrate e sulla consecutiva rigenerazione della parete vescicale, Arch. ital. di urol. **10**:3 (Jan.) 1933.

can be done even when the entire wall of the bladder, except the trigone with the ureteral orifices, is involved. The resection may be followed by suture, or suture may not be employed; even in the latter case, the bladder regenerates completely. A case in which Redi operated is of particular interest from the surgical standpoint, in that partial resection of the bladder was accomplished suprapubically by use of the electric knife. The tumor, which was composed of highly typical cells, involved the entire left half of the bladder; it was limited posteriorly by the ureteral orifice and anteriorly by the median line of the organ. When it was seen that the ureteral orifice was not invaded by the tumor, Redi preserved it, although he extensively coagulated this area. The entire left half of the bladder was removed, and the remainder of the cavity was packed around a permanent catheter. Two weeks later, where the left half of the bladder had been, a smooth, shiny, pinkish wall had been developed, differing markedly from the mucosa. By the end of a month there was a well defined left vesicular cavity, rather more extensive than the right half. There was no ureteral reflux, and the general condition of the patient was excellent. When the report was written, one year had passed since the operation, and there had been no sign of recurrence.

Marri, who made the pathologic examination of the specimen, found complete absence of epithelial pearls or of any tendency to cornification, which showed that the growth was highly malignant. Absence of cornification is one of the characteristics of those forms which ulcerate readily, spreading through the walls of the bladder and extending to adjacent structures. That the tumor was of definitely infiltrative type, however, is shown by the fact that the vesical wall itself was irregularly invaded in every direction by the epithelial extensions; the invasion stopped just short of the peripheral portions of the wall. Examination of tissue from the newly formed vesical wall, on the sixtieth day following operation, revealed regeneration that included all the walls, thus proving that for such a result it is not necessary to make use of a suture for the purpose of reconstructing a vesical cavity. In some tracts the epithelium was completely reconstituted; in some places it was identical with normal epithelium, and in the other areas nearly so. The elements were roundish, thick-set and rather large, evidently following a biologic law common to the various tissues in these cases, but not to be confused with pathologic processes of proliferation with which it had no relation. Amitotic division was observed everywhere, but never mitosis. The histologic observations led to the conclusion that this regeneration had come from the margins of the urinary bladder remaining after resection of the diseased portion. The regeneration applied to all strata of the wall, muscular and mucosal.

Godard and Koliopoulos,[44] although they expressed belief in the usual methods of treatment of carcinoma of the bladder of women, advised cystectomy in cases in which ordinary methods are impracticable. Cystectomy is logical only when combined with total hysterectomy; a bloc formed of the bladder, uterus, related lymphatic regions and vesicovaginal zone corresponding to the trigone should be removed in one piece.

An operation in two stages is done. The first stage is bilateral cutaneous iliac ureterostomy by Papin's method. This preliminary step has also the advantage of permitting exploration of the condition of the kidneys and ureters, which will reveal whether cystectomy is feasible. Preoperative care consists of lavage of the bladder, administration of vaccine and, when there has been profuse hematuria, transfusion.

Cystectomy is indicated for malignant tumors of the floor of the bladder, tumors of the trigone and most tumors of the lateral surface of the bladder. Partial cystectomy is nearly always insufficient, but may be done for early carcinoma of the dome of the bladder. One should be certain that the carcinoma is not secondary.

The final operation is performed in stages: First, the adnexa are removed, and the utero-ovarian and round ligaments are tied. Second, the umbilico-uterine arterial trunk is isolated and tied, and the uterosacral ligament is sectioned. This second stage is accomplished by dissection of the umbilical artery, freeing of the origin of the uterine artery, and tying of the common trunk above the latter. In exceptional cases the hypogastric artery must also be tied. As soon as section of the uterosacral ligament is accomplished, the uterus becomes movable and rises easily. Third, the neck of the bladder is liberated and sectioned. Fourth, the vagina is sectioned. Fifth, peritonization is performed, followed by the placing of a vaginal drain. A suture is drawn from right to left, uniting the prevesical peritoneum to the sigmoid part of the colon.

The survival of patients, as reported by various authors in cases in which cystectomy has been performed, is as follows: five years and four years (Heresco), eight years (Nicholitch), five years (Wolff), from one to six years in 6 cases (Albarran), from two to six years (Werhogen) and sixteen years (Pawlick). Watson, in 16 of 62 cases had cures lasting "several years." Simon reported 2 cases in which the ureters were implanted into the intestine, with 1 death from postoperative uremia and 1 death three months later. Beer reported that five years after total cystectomy he had observed recurrence of the malignant growth in the iliac region.

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44. Godard, Henri, and Koliopoulos, A.: La cystectomie totale chez la femme dans le cancer de la vessie, Rev. de chir., Paris **70**:201 (March) 1932.

Cystectomy, despite its gravity, is indicated for epitheliomas and sarcomas that resist physical agents; exceptionally, also, in the course of a Wertheim operation for carcinoma of the uterine cervix, when one encounters invasion of the floor of the bladder and has to operate in a single stage.

Chwalla [45] concluded, from his experience with vesical carcinomas, that with the exception of those carcinomas which involve the base and neck of the bladder, it is best to resect all, since cure is thus more likely. Although Chwalla's operative results are not unusual, he has achieved a large number of apparent cures; 40 per cent of the patients have had no recurrence eight years after operation. In cases of carcinoma of the base of the bladder, Chwalla stated that he treats only symptomatically or not at all. If the carcinoma is obstructive, a suprapubic fistula is made. He expressed the belief that cystectomy, as judged by the results reported, is hardly justified at present. He also gives as his opinion that the best results and improvement in the future will rest on early diagnosis and early operation. An early diagnosis is possible; every patient with hematuria should undergo cystoscopy, and every patient with urinary disturbance should be examined urologically.

Barringer [46] stated that from 30 to 55 per cent of carcinomas of the bladder can be controlled by proper irradiation for three years or more. He reported 129 cases. In 98 cases, the clinical diagnosis was supported by biopsy. In this group, 52.9 per cent of 51 patients with papillary carcinomas and 29.7 per cent of patients with infiltrating carcinomas of the bladder were alive without evidence of disease at the end of three years.

Barringer advocated suprapubic cystotomy and implantation of radon seeds in the treatment of carcinoma of the bladder. He used gold seeds of radon, containing from 1 to 1.5 millicuries. He implanted a gold seed in each square centimeter of the base of the tumor. His operative mortality was only 4 per cent in 109 consecutive cases. He expressed the belief that it is possible to control from 10 to 15 per cent of carcinomas of the prostate gland for three years or more by irradiation. If the disease is confined to the posterior region of the prostate gland, between the fascial planes, without involvement of the vesical neck, the use of radon needles, implanted through the perineum, is advised. In cases in which the tumor involves the neck of the bladder, cystotomy and implantation of gold seeds of radon into the prostatic tumor are preferable.

45. Chwalla, Rudolf: Das Carcinom der Harnblase und der gegenwärtige Stand seiner Behandlung, Ztschr. f. urol. Chir. **35**:251, 1932.

46. Barringer, B. S.: Bladder and Prostatic Carcinoma, J. M. Soc. New Jersey **29**:115 (Feb.) 1932.

Sauer [47] reported a case of endometriosis of the urinary bladder. The patient was a woman, aged 40, who had severe dysuria and hematuria for nine months. Cystoscopy revealed a mass, the size of a cherry, on the posterior wall of the bladder in the median line. It protruded into the bladder and was surrounded by a region of bullous edema. There was no definite inflammation in the bladder or around the tumor. The patient was operated on, and the tumor was removed with wide resection. It was thought at the time of operation, judging from the consistency and appearance of the tumor, that it unquestionably was malignant. Microscopic examination revealed typical endometriosis.

Diverticulum.—Spinelli [48] stated that although most diverticula of the bladder are acquired, a small number are evidently congenital, for they are found in fetuses and associated with other malformations. They increase in frequency with the age of the patients, reaching their maximal frequency in the fifth or sixth decade of life. They are rare among women, and it is significant that they develop in the same decades as obstructions of the bladder and urethra from various causes.

In order of importance, the site of diverticula is: first, the lateral walls of the bladder; second, the floor of the bladder; third, the ureteral and periureteral regions, and fourth, the dome and posterior wall. This distribution is based on anatomic findings of points of lessened resistance to continued increase of pressure, which yield and permit cellules and diverticula to form.

When the normal habitual force necessary to empty the bladder has become increased by conditions which obstruct the normal outflow of urine, the mechanism of production of diverticula becomes evident. Lesions which cause obstruction to the outflow would act pathologically as follows: first, through insufficient emptying of the bladder, resulting in urinary stasis; second, through the effort of the detrusor to overcome the obstruction; third, through the distention and atony which injure the detrusor in cases of incomplete chronic obstruction; fourth, through the tendency of the stagnant urine to become infected, and fifth, through incoordinated and violent contractions to which the bladder is subjected after cystitis has developed. Under any of the conditions named, the muscle attempts vigorously to overcome the obstacle. This is followed by hypertrophy of the musculature and a characteristic appearance of the bladder in columns, with marked weakness of the walls, especially at the points of congenital inferiority. It is just at these points that the mucosa of the bladder tends to open between the trabeculae of the columns or between the openings of the meshes, while

47. Sauer, H.: Ueber einen Fall von Endometriose der Harnblase, Zentralbl. f. Gynäk. **57**:347 (Feb. 11) 1933.

48. Spinelli, Antonino: I. Diverticoli della vescica, Policlinico (sez. chir.) **39**: 390 (June 15) 1932.

the process of inflammation which always accompanies these lesions, infiltrating the muscular wall, renders it less elastic and more liable to give way. Thus the diverticulum begins, and as the pressure increases, it gains in size. The wall is soon infiltrated by the inflammatory process, which produces abundant connective tissue of a poor sort, almost always devoid of elastic and muscular fibers, while on the outside the inflammatory process extends by contiguity to the nearby parts and forms cicatricial bridles which also impair the elasticity of the same wall.

The diverticulum becomes evident only when complications arise. The functional symptoms most frequently met are dysuria, retention, interrupted micturition and terminal pyuria; on these the diagnosis is based. Left to itself, the diverticulum grows larger, and may give rise to four types of complications: mechanical, infective and inflammatory, calculous and neoplastic, and ascending disturbances. Spinelli uses the suprapubic route as the most convenient approach to a diverticulum of the bladder. The postoperative course after removal is generally good. The mortality rate, according to various authors, is 9.91, 10 and 13 per cent; functional insufficiency remains in about 20 per cent of the cases.

Rupture.—Mark [49] observed the innocuousness of mediums for intravenous urography, and suggested their use in the diagnosis of ruptured bladder. He stated that 35 cc. of 40 per cent skiodan was given intravenously while the patient was on a Bucky diaphragm. Seven minutes following the start of the injection, the first roentgenogram was taken and eight minutes after the injection was started, the second was taken. These roentgenograms disclosed extraperitoneal rupture into the space of Retzius, with most marked extravasation on the left. The patient was immediately taken into the operating room, the diagnosis substantiated and repair instituted.

Mark stated that use of this method in cases of suspected rupture of the kidney of lesser degree and in cases of suspected rupture of the bladder is simple and innocuous, and should apply to both intraperitoneal and extraperitoneal rupture. It appears to be free from the objectionable features that might be held against the usual methods of diagnosis.

Hernia.—Oberlin [50] found, in the literature, reports of only 13 cases of perineal hernia of the bladder, to which he added the report of a case of his own. Of the entire 14 patients, 10 were females. There are two types of perineal hernia, median and lateral. The median type, due to abnormal depth of Douglas' culdesac, pressing either on the wall of the

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49. Mark, E. G.: Intravenous Urography in the Diagnosis of Rupture of the Bladder, J. A. M. A. **100**:42 (Jan. 7) 1933.

50. Oberlin, Serge: Hernie périnéale de la vessie, Bull. et mém. Soc. nat. de chir. **58**:1237 (Oct. 19) 1932.

rectum or on that of the vagina, comprises both hydroceles and elytro-
celes. Lateral hernias, on the contrary, emerge through the fibers of
the levator ani or insinuate themselves between this muscle and the
ischiococcygeal muscle. The position of the hernia with reference to
the transverse perineal muscle is difficult to establish, since it is hardly
visible, owing to the pushing back or distortion of this muscle by the
development of the hernia. Anterolateral perineal hernia had been
reported only in the male; it is caused by trauma and does not, properly
speaking, constitute a true hernia. Apart from these, all perineal
hernias of the bladder are posterior; however they may begin, they
end by passing behind the urogenital diaphragm and taking a position
between the anus and the ischium.

In Oberlin's case, the hernia, coming from the small pelvis, passed
obliquely backward, crossing the axis of the vagina. A series of roent-
genoscopic and roentgenographic views indicated that the content of the
sac was not intestine or omentum. Because the swelling was easily
reducible, the diagnosis of cold abscess was excluded; a diagnosis of
hernia of the bladder was made. This hernia was constituted by a
prolongation of the bladder that communicated widely with the rest of
the organ, and in no sense formed a diverticulum. It was accom-
panied by a sort of funnel that replaced the trigone. The bladder was
of normal capacity, but was much deformed in contour; it was flattened
transversely, with the two lateral walls almost vertical and very close
together. On the sides of the funnel the two ureteral orifices could
be seen, in normal condition. There was no interureteral muscle; the
funnel stretched out behind the orifices, which seemed nearer to the
neck of the bladder than is usual. The levator muscle was represented
by only a few fibers, stretched out and atrophied, on the surface of the
hernia. A sound introduced through the urethra and bent downward
and to the left easily penetrated the herniated portion of the bladder
and could be felt on palpation.

To push the pocket back into position was simple. It was much
more difficult to reconstruct the floor of the perineum, in view of the
poor quality of the tissues available for use. Oberlin could make a
reconstruction only in a single layer, taking in the gluteus maximums
and a few remnants of the levator ani and fixing them within the wall
of the vagina. Thus, an insecure curtain was drawn under the bladder,
and the skin was sutured over a horsehair drain. The results were
excellent for two years, after which the hernia recurred. It was a
remarkable fact that the patient had never suffered the least incon-
venience in function of the bladder throughout the history of the hernia.

[COMPILERS' NOTE.—Perineal hernias of the bladder are extremely
rare. They are more commonly observed among females than among

males. The condition must be distinguished from rectocele, cystocele and other ectopic conditions of the lower part of the urinary tract. In a review of 15 cases of diverticulum of the urinary bladder associated with hernia, tabulated by Lowsley and Gutierrez,[51] not a single instance of this perineal type of hernia is mentioned. It is obvious that it is most important to establish a correct diagnosis of this acquired or congenital lesion previous to its surgical repair; accurate diagnosis can be aided by the routine use of cystography.]

Function.—Smith and Engel[52] came to the conclusion that the normal motor function of the bladder is maintained by balanced innervation from the sympathetic and the parasympathetic nerves. The parasympathetic nerves are capable of carrying on vesical function independently, and the action of the sympathetic nerves on the sphincteric outlet is brakelike, relatively speaking, a retarding balance against the action of the parasympathetic nerves.

Retention or incontinence must be considered in the following respects: first, as to whether retention is the result of anatomic obstruction, or defective innervation, which must be determined by cystoscopy and cystography; second, as to whether incontinence is the result of overflow of retained urine or a complete absence of sphincteric control; third, as to which division or part of the autonomic nerve supply is affected. Smith and Engel stated that personal experience and a survey of current literature indicated that in most instances responsibility for either incontinence or retention can be placed on faulty innervation from the parasympathetic nerves, which in most instances is associated with osseous fusional defects of the lower part of the spinal column, in which the nerve roots have become involved in associated fibrous tissue during the development of the patient. In cases of retention, degeneration of the parasympathetic nerves apparently leaves the brakelike innervation from the sympathetic nerves in control of the sphincters. Smith and Engel stated that in cases of incontinence the inherent tonus of the sphincter muscles, which is dependent on parasympathetic innervation, was absent from the first in the more aggravated cases, and had been completely lost during the degenerative process, in which primary retention had passed over into incontinence.

Smith and Engel stated that treatment is regarded as essentially surgical. Correction of impingement on nerves involved in osseous spinal defects should receive primary consideration. In cases of incontinence, reenforcement of sphincteric control should be attempted by

51. Lowsley, O. S., and Gutierrez, Robert: Operative Intervention for Relief of Diverticulum of the Urinary Bladder, Analysis of Fifty-Four Cases, J. Urol. **19**:459 (April) 1928.

52. Smith, C. K., and Engel, L. P.: Neurogenic Vesical Dysfunction in Children, J. Urol. **28**:675 (Dec.) 1932.

transplantation of muscles into the perineum, encircling the urethra, or by plastic tightening of the vesical sphincteric outlet. If a sense of filling or emptying of the bladder remains, fair to good results can be expected. On the contrary, if no such sense remains this plan is useless. In cases of retention, resection of the sympathetic chain releases the brakelike action on the sphincter, and good emptying power can be expected.

Cumming [53] stated that observations made on the urinary tract by means of serial roentgenograms, together with the usual functional studies and, in some instances, cystoscopic procedures carried out primarily for treatment, indicate that emptying of the bladder can be established following retention due to injury of the spinal cord or to pressure, as from a tumor, without the use of catheters. In stubborn cases automatic emptying can be facilitated by the use of caudal anesthesia. In case of infection of the bladder, ascending involvement of the kidneys and ureters is universal, and a large proportion of patients who survive the early effects of a lesion of the spinal cord succumb to renal infection. In some instances there seems to be more or less spontaneous recovery from renal infection, but recurrences are frequent. In the presence of gross infection of the urinary tract, with a paralyzed bladder, a great deal can be accomplished toward overcoming or curing this infection by means of routine, accepted types of treatment. Prolonged drainage by a ureteral catheter is particularly efficient. Cumming stated that hydronephrosis is not a common sequel of paralysis of the bladder, nor is ureteral atony a common finding except in the presence of gross infection.

Learmonth and Braasch [54] considered the value of sympathetic neurectomy in vesical conditions. They drew attention to what seemed to them to be a significant fact, as far as their material allowed them to judge. Cases are found in each of the three groups in which section of the presacral nerve alone was effective, either as a primary operation or after local procedures had failed. They expressed the opinion, therefore, that in suitable cases the possibility of using this procedure should be considered. As time passes, no doubt the indications for the operation will be more strictly defined, and this may mean either restriction of its field or expansion to include other conditions. The authors expressed themselves as being satisfied that the procedure had occasional value in their own practice.

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53. Cumming, R. E.: Structural and Functional Changes in Urinary Tract Following Focal Cord Lesions, J. A. M. A. **99**:1998 (Dec. 10) 1932.

54. Learmonth, J. R., and Braasch, W. F.: Clinical and Surgical Aspects of Nerve Lesions Involving the Lower Part of the Urinary Tract, Ztschr. f. urol. Chir. **36**:195 (Jan.) 1933.

Tumor.—Zondek [55] has studied the behavior of the anterior hypophyseal hormone in 14 cases of teratoma of the testis; the ages of the patients varied from 30 to 66 years. He pointed out that the excretion of prolan A by patients with tumors is usually somewhere between a physiologic minimum and the greatly increased excretion found in pregnancy. (Embryonal adenocarcinoma and chorionepithelioma of the testis result in the excretion of from two to five times the amount of anterior hypophyseal hormone found in pregnancy.)

Control tests were made on the urine of healthy men and on that of men with various types of internal disease. In all, the reaction was negative. In view of this, Zondek concluded that in men a positive reaction may be interpreted as evidence of a malignant tumor of the testis.

Zondek stated that it may be possible to demonstrate a definite relationship between the excretion of prolan A in the urine and the type of testicular tumor; he points out the wide variation in the amount excreted in cases of chorionepithelioma and of teratoma. He closed his study with a plea that the urine of patients suffering from testicular tumors be regularly examined for the hormone of the anterior hypophysis.

Bollag [56] stated that malignant tumors of the testis occur most frequently between the ages of 25 and 35 years. The most frequently observed etiologic factors are ectopia of the testis and trauma. Earlier therapeutic methods consisted chiefly in simple castration or radical operation, including removal of the pelvic and abdominal lymph nodes. Since 1923 more patients are being treated by extirpation of the primary tumor with postoperative irradiation. The author found in the literature reports of 47 cases in which results were satisfactory.

Although the last ten years have shown progress in studies of the etiology and treatment of testicular tumors, there is still an important field for investigation of these tumors from the point of view of hormones. In this connection, Zondek has urged study of the anterior hypophyseal hormone. In several cases, chiefly cases of chorionepithelioma of the testis, but including also 5 cases of testicular sarcoma, the hormone was demonstrated. The demonstration can be made by injection of the urine or extracts therefrom (after the technic of Zondek), or by the implantation of fragments of tumor into immature female mice.

55. Zondek, Bernhard: Maligne Hodentumoren und Hypophysen Vorderlappenhormone, Klin. Wchnschr. **11**:274 (Feb.) 1932.

56. Bollag, Louis: Zur Kasuistik der malignen Hodentumoren, Schweiz. med. Wchnschr. **62**:419 (April) 1932.

The author reported 2 cases of seminoma in which the hormone of the anterior lobe of the hypophysis was demonstrated.

PENIS

Carcinoma.—Leighton [57] made a summary of 67 cases of carcinoma of the penis. Of the 24 patients who refused treatment, 1 died of carcinoma and 1 of an unknown cause; 19 had not been heard from, and 1 was operated on elsewhere. Of 43 patients treated conservatively, 4 received roentgen or radium therapy. Three of these died and 1 was not traced. Of 34 cases in which operation was performed, partial amputation was done in 3 cases, and partial amputation with inguinal dissection in 5 cases. Total amputation was done in 1 case.

Of 11 patients who were subjected to total amputation with inguinal dissection, 3 died. Total emasculation was done in 14 cases; 2 of the patients could not be traced, and 9 of the remainder died.

Five of the 34 patients operated on had not been heard from; 14 died, 2 postoperatively and 3 of recurrence; 9 lived from one month to eighteen years, and died of other causes than carcinoma. Nineteen patients were living for from six months to twenty-five years after operation. In each of the 3 cases in which death occurred from recurrence, there was metastasis in the inguinal lymph nodes at operation. Five patients whose tumors were of grade 2, and who had inguinal metastasis at the time of operation, were still alive and free from recurrence at the time of the study.

[COMPILERS' NOTE.—Papillary or flat carcinoma of the penis, usually arises beneath a tight, redundant prepuce. The value of the prophylactic procedure of circumcision in youth cannot be too greatly emphasized. Advocates of radical operation, such as the procedure outlined by Young, and of roentgen therapy, vie with one another in reporting excellent end-results. Increasing evidence shows the superiority of radium treatment if applied early and before invasion of Buck's fascia. Here again the prognostic importance of the grade of malignancy in determining the probability of cure, or of the length of life after any form of treatment, is noteworthy.]

UROGRAPHY

Wesson and Fulmer [58] stated that pyelography after intravenous injection should be used in any case in which the presence of stone in the ureter is suspected. If the medium is eliminated equally well from

57. Leighton, W. E.: Carcinoma of the Penis, with a Report of Sixty-Seven Cases, Am. J. Cancer **16**:251 (March) 1932.

58. Wesson, M. B., and Fulmer, C. C.: Influence of Ureteral Stones on Intravenous Urograms, Am. J. Roentgenol. **28**:27 (July) 1932.

both kidneys, no stone is present. This type of pyelography is not of direct value in the diagnosis of obstructing ureteral stones which do not cast shadows, but is of distinct value in excluding stones from the diagnosis. In cases of acute ureteral stone, the pyelogram on the unaffected side will be good, and on the affected side, evidence of increased density of the kidney but no outline of the pelvis or ureter, or a very much delayed one, will be seen.

The authors stated that in the presence of ureteral stones that partially block the ureter and cause stasis and hydronephrosis, the pelvis is usually well outlined. If the stone blocked the ureter completely, there would be a functionless kidney above, and hence no pelvic shadow. The early reflex inhibition from ureteral irritation acts to protect the kidney from early hydronephrosis. The reduction in ability to secrete the medium is apparent rather than real. The increased density of the affected kidney indicates that there is a concentration of the medium between the glomeruli and the distal end of the connecting tubules, the medium being of equal concentration in the blood of both kidneys.

URINARY INFECTION

Campbell,[59] after reviewing 274 of his own cases of chronic pyuria in juvenile patients, stated that under the diagnosis of chronic pyelitis or chronic cystitis, infants and children are commonly and unsuccessfully treated for months or years. When renal infection exists, the lesion is basically suppurative pyelonephritis. In many cases of so-called pyelitis, the infection is localized in the bladder and urethra. When chronic urinary infection resists intensive medical treatment for one month, a complete urologic examination is indicated. Campbell has found, in infants and children, almost every lesion of the urinary tract which one is accustomed to associate with adult life. As a rule, medical treatment alone is inadequate to effect bacteriologic cure, and while surgical attack may serve only to control rather than to cure the infection, conservative operations often will prevent further renal destruction and thus prove life-saving. Occasionally, nephrectomy is demanded.

May[60] stated that infestation with Trichomonas, which is rather common in the vagina, is only rarely found in the urinary tract. He cited the case of a man, aged 51, who had a pain in the right renal region. He had no urinary disturbances, urethral discharge or hematuria. Physical examination gave essentially negative results. Following thorough irrigation of the urethra and bladder, the prostatic

59. Campbell, M. F.: Chronic Urinary Infection in Infancy and Childhood, J. A. M. A. **99**:2231 (Dec. 31) 1932.

60. May, Ferdinand: Trichomonas vaginalis-Infection der Harnwege, Ztschr. f. urol. Chir. **35**:213, 1932.

secretion contained pus cells and Trichomonas vaginalis. There were a few leukocytes and Trichomonas vaginalis in the urine.

The author was unable to find in the literature a report of a similar case affecting a male and only a few in which the urinary tract of a woman was infested with Trichomonas.

URINARY ANTISEPSIS

Davis and Sharpe [61] stated that hexylresorcinol (dose, 0.75 Gm.) exerts an irregular and transient antiseptic action in about one third of the four hour samples. Methenamine (dose, 1 Gm.) is comparatively more efficient than either pyridium or hexylresorcinol in causing the normal person to secrete urine which is antiseptic against both the colon bacillus and the staphylococcus. Acriflavine (dose, 0.2 Gm.), administered in capsules, exerts a surprisingly uniform and consistent antiseptic action in normal urine against both the colon bacillus and the staphylococcus. Urinary alkalinity is essential. On the other hand, acriflavine (dose, 0.2 Gm.), administered in shellac-coated pills, is practically inert. The acriflavine administered in capsules, although not injurious in efficient doses, causes unpleasant symptoms (nausea and catharsis) in a fairly large proportion of cases. Consequently, acriflavine has its definite clinical limitations. Clinical experience indicates, however, that this drug is of distinct value in selected cases, particularly those of acute infection of the urinary tract.

Davis and Sharpe concluded that, as determined by antiseptic tests of samples of urine obtained before and after administration in unit maximal dosage to normal persons, pyridium is practically inert, hexylresorcinol is slightly antiseptic, methenamine is efficient and acriflavine (in alkaline urine) is unfailing.

Davis and Sharpe stated that in the treatment of infections of the urinary tract, the time has not yet arrived when the old reliable methods, based on detailed investigation and elimination of the accessory or underlying causes, may be discarded in favor of indiscriminate medication.

UROLOGIC BACKACHE

Morris, Langlois and Brunton,[62] in a review of 3,600 histories, found backache of urologic origin in 1,127 cases (31 per cent). In this group there were 620 female and 507 male patients. The majority of patients with chronic renal lesions refer to their disability as backache and not as pain in the back. The backache of pyelitis is a constant,

61. Davis, Edwin, and Sharpe, J. C.: Urinary Antisepsis, J. A. M. A. **99**:2097 (Dec. 17) 1932.

62. Morris, H. I..; Langlois, L. J., and Brunton, J. F.: Urologic Backache, J. A. M. A. **99**:2237 (Dec. 31) 1932.

dull, deep-seated ache, diffusely felt in the lumbodorsal region. The backache of ptosis is similar to that of chronic pyelitis, but in addition is of a dragging character and is relieved by rest. The disability in renal calculous disease is not true backache, but a persistent, paroxysmal pain in the costovertebral region, which is intensified and radiates as the calculus passes through the ureter. Prostatic backache is a dull, aching, sacral disability, which is most severe on rising and is occasionally referred along the course of the sciatic nerve.

HYPERINSULINEMIA SECONDARY TO AN ADENOMA OF THE PANCREAS

REPORT OF A CASE WITH OPERATIVE CURE

LLOYD I. ROSS, M.D.

AND

JOHN M. TOMASCH, M.D.

CLEVELAND

Since the liberation of insulin, by the monumental work of Banting and Best[1] in 1922, the clinical syndrome of hypoglycemia or insulin shock has become a well recognized medical entity and one with which the average clinician is now fully familiar.

That such a state, so-called hyperinsulinemia, might arise spontaneously within the human body as a result of the overproduction of insulin by the cells of the islands of Langerhans was first suggested by Harris[2] in 1924.

Krause,[3] Marsh,[4] Gammon and Tenery,[5] and Heyn[6] have reported cases presenting the clinical picture of recurrent hypoglycemia in which the blood sugar values during the attacks ranged from 33 to 60 mg. per hundred cubic centimeters.

Since none of the foregoing cases has come to autopsy or been surgically explored, the hypoglycemia cannot be irrefutably ascribed to hyperinsulinemia resulting from hyperplasia or tumorous proliferation of the islet cells.

Finney and Finney, Jr.,[7] and Allan[8] reported two cases in which the symptoms of hyperinsulinemia were present, but at operation no

1. Banting, F. G., and Best. C. H.: The Internal Secretion of the Pancreas, J. Lab. & Clin. Med. 7:251, 1922.

2. Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. 83:729 (Sept. 6) 1924.

3. Krause, F.: Hyperinsulinism with Hypoglycemic Syndrome, Klin. Wchnschr. 9:2346, 1930.

4. Marsh, H. E.: Hyperinsulinism with Report of Cases, Wisconsin M. J. 30:340, 1931.

5. Gammon, G. D., and Tenery, W. C.: Hypoglycemia; Clinical Syndrome, Etiology and Treatment; Report of Case Due to Hyperinsulinism, Arch. Int. Med. 47:829 (June) 1931.

6. Heyn, Louis G.: Hyperinsulinism. J. A. M. A. 98:1441 (April 23) 1932.

7. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, Ann. Surg. 88:584, 1928.

8. Allan, F. N.: Hyperinsulinism, Arch. Int. Med. 44:65 (July) 1929.

gross abnormality of the pancreas was found. In each case a portion of the pancreas was resected. It was believed that there was some amelioration of the patients' symptoms.

The association of hypoglycemic manifestations with marked hypertrophy of the islands of Langerhans has been demonstrated by the cases reported by Phillips [9] and Gray and Feemster.[10]

Warren,[11] in 1926, noted the occurrence of tumorous proliferation of the islet cells during his microscopic studies of pancreatic sections but failed to attach any clinical significance to the presence of these adenomas.

Wilder and his associates [12] at the Mayo Clinic correlated this tumorous proliferation of the islands of Langerhans with the clinical syndrome of hypoglycemia.

Thalhimer and Murphy,[13] McClenahan and Morris,[14] Frank,[15] and Smith and Seibel [16] reported four additional cases which presented the clinical picture of hypoglycemia. In each instance, autopsy revealed a definite adenoma in the pancreas composed of island tissue.

The available literature presents three cases reported by Howland and co-workers,[17] Carr and his collaborators,[18] and Womack and his associates,[19] in which a preoperative diagnosis of hyperinsulinemia, with hypoglycemia, secondary to a tumor involving the islands of Langerhans has been confirmed by the demonstration of the tumor and its enucleation

9. Phillips, A. W.: Hypoglycemia with Hypertrophy of the Islands of Langerhans, J. A. M. A. **96**:1195 (April 11) 1931.

10. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child of a Diabetic, Arch. Path. **1**:348 (March) 1926.

11. Warren, S.: Adenomas of the Islands of Langerhans, Am. J. Path. **2**:335, 1926.

12. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, J. A. M. A. **89**:348 (July 30) 1927.

13. Thalhimer, W., and Murphy, F. D.: Carcinoma of the Islands of the Pancreas, J. A. M. A. **91**:89 (July 14) 1928.

14. McClenahan, W. U., and Norris, G. W.: Adenoma of the Islands of Langerhans with Associated Hypoglycemia, Am. J. M. Sc. **177**:93, 1929.

15. Frank, H.: Fatal Hypoglycemia in Adenoma of the Pancreas, Deutsches Arch. f. klin. Med. **171**:175, 1931.

16. Smith, M. G., and Seibel, M. G.: Tumors of the Islands of Langerhans and Hypoglycemia, Am. J. Path. **7**:723, 1931.

17. Howland, G.; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: Dysinsulinism, J. A. M. A. **93**:674 (Aug. 31) 1929.

18. Carr, A. D.; Parker, Robert; Graves, E. W.; Fisher, A. O., and Larrimore, J. L.: Hyperinsulinism from B-Cell Adenoma: Operation and Cure, J. A. M. A. **96**:1363 (April 25) 1931.

19. Womack, N. A.; Gnagi, W. B., Jr., and Graham, E. A.: Adenoma of the Islands of Langerhans with Hypoglycemia, J. A. M. A. **97**:831 (Sept. 19) 1931.

at the time of operation with complete restoration of normal carbohydrate metabolism during the postoperative interval.

Cushing,[20] in his Lister Memorial Lecture, referred to a case of hyperinsulinemia secondary to an adenoma of the pancreas that was then under observation at the Peter Bent Brigham Hospital. The details of this case are, we understand,[21] now being prepared for publication.

REPORT OF CASE

The case which we wish to report first came under our observation on Oct. 13, 1931.

History.—A. R., a 33 year old Mexican, was brought into the accident ward of Cleveland City Hospital with the following history: At 7 p. m. the night before he had been picked up from the street by the police as an "alcoholic" and taken to the station house overnight. He had apparently fallen, striking his head on the sidewalk, for he had a contusion over his right eye and was in a semiconscious state when first found. He failed to regain consciousness during the night, however, and was therefore brought to the hospital.

Physical Examination.—The patient was a stuporous, middle-aged Mexican, who responded to questions only by mumbling. There was a contusion over the right eye with a small hematoma, but no laceration of the scalp. There was no evidence of hemorrhage from the cranial orifices. The pupils were moderately dilated and slightly unequal, the right being larger than the left. Reaction to light and accommodation was only slight. The eyegrounds were normal. There was no nuchal rigidity. The heart and lungs were normal. Blood pressure was 112 systolic and 52 diastolic. Examination of the abdomen, genitalia and rectum revealed no abnormalities. The reflexes were physiologic except the Babinski, which showed bilateral dorsiflexion of the great toes without flaring of the other toes.

Laboratory Data.—On admission the urine was normal. The hemoglobin was 100 per cent, and the white blood count 16,000. The temperature was 37.2 C. (98.9 F.), the pulse rate, 80, and the respirations, 20. Spinal puncture yielded a clear fluid, with a pressure of 2 mm. of mercury, which contained 2 cells. The Pandy test was negative.

The patient could not be aroused from his semistupor, and diagnosis of alcoholism with cerebral edema (?) and fracture of the skull was made.

As a means of combating the supposed cerebral edema, hypertonic dextrose was given intravenously. The patient instantaneously aroused from his stupor, sat upright, and appeared to be entirely rational. Questioning failed to elicit any history of previous similar attacks. No history of diabetes or insulin usage could be obtained.

On the morning of the day after admission the patient was again in coma. Chemical examination of the blood at that time showed a blood sugar of 23 mg. per hundred cubic centimeters, urea of 32 mg., creatinine of 1.9 mg. and a carbon dioxide-combining power of 60. Dextrose was given intravenously with the same phenomenal effect. A tentative diagnosis of hyperinsulinemia, with hypoglycemia, secondary to a tumor of the islands of Langerhans was then made.

20. Cushing, Harvey: Lister Memorial Lecture, Lancet 2:119, 1930.
21. Cushing, Harvey, and Newton, F. C.: Personal communications.

Blood was withdrawn at three hour intervals during the day; no food was given other than dextrose administered intravenously. The blood sugar levels are recorded in table 1.

The patient was then placed on a measured diet of 1,800 calories, carbohydrate 60 Gm., protein 60 Gm., fat 140 Gm. On this diet he continued to go into hypoglycemic shock at six to eight hour intervals.

During each of these seizures the patient showed the plantar response first called to our attention by Hart and Bond [22] as a diagnostic aid in differentiating between insulin shock and diabetic coma. In their experience this extensor response was not elicited during diabetic coma unless the patient had some associated organic disease involving the pyramidal tract. In insulin shock, on the other hand, the extensor response had been obtained in two instances. They conclude, therefore,

TABLE 1.—*Initial Blood Sugar Values*

Time	Blood Sugar Level, Mg. per 100 Cc.	Intravenous Dextrose, Gm.
8:00 a.m.	23	25
12:00 noon	43	
3:00 p.m.	23	25
6:00 p.m.	88.4	
9:00 p.m.	28.6	25

TABLE 2.—*Initial Dextrose Tolerance Test*

Time	Blood Sugar Level, Mg. per 100 Cc.	Intravenous Dextrose, Gm.
7:15 a.m. (fasting specimen)	25	25
7:45 a.m.	76	
8:15 a.m.	229	
8:45 a.m.	205	
9:15 a.m.	210	
9:45 a.m.	216	
10:15 a.m.	195	
10:45 a.m.	137	

that the presence of the plantar response in a comatose diabetic person on insulin treatment should be accepted as evidence that the coma is due to insulin shock.

A dextrose tolerance test (table 2) was done on October 16. This, as in the recorded cases, showed a diabetic type of curve. Urinalyses, however, failed to reveal any sugar or acetone in the urine.

A study of the gastro-intestinal tract was made in an attempt to visualize a pancreatic tumor. The fluoroscopic examination and films of the stomach and duodenum showed no evidence of an organic lesion within these viscera or of displacement by an extra gastric growth.

Pituitary dysfunction, as a cause of the recurrent hypoglycemia, was eliminated by the roentgenologic demonstration of a normal sella turcica and the absence of any clinical evidence of pituitary dystrophy.

Plates of the skull showed no evidence of fracture.

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22. Hart, P. M. D'A., and Bond, H. P.: The Diagnostic Value of the Plantar Response in Insulin *Coma*, Brit. M. J. **1**:895 (May 18) 1929.

In order to prove that the hypoglycemia was not due to inadequate glycogen in the liver, 1 cc. of epinephrine hydrochloride was given subcutaneously on October 21. The response is recorded in table 3.

It now seemed reasonably well established that this man's symptomatology was due to a persistent hyperinsulinemia. An exploratory laparotomy was, therefore, advised.

In preparation for operation, 1,500 cc. of 5 per cent dextrose was given subcutaneously and 100 cc. of 50 per cent dextrose intravenously.

Operation and Course.—An exploratory laparotomy was done by Dr. S. O. Freedlander on November 2 with the patient under spinal anesthesia. When the pancreas was exposed a small, purplish, cystlike structure, 1.5 to 2 cm. in diameter, was found projecting from its anterior surface about a half inch above the inferior border of that organ near its midportion. The remainder of the pancreas was

TABLE 3.—*Preoperative Response to Epinephrine*

Time	Blood Sugar Level, Mg. per 100 Cc.	Medication
1:45 p.m.	44	1 cc. epinephrine hydro- chloride subcutaneously
2:15 p.m.	63	
2:45 p.m.	49	

TABLE 4.—*Daily Postoperative Blood Sugar Levels*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
11/2/31..............	99	Immediately postoperative
11/3/31......	151	Fasting
11/4/31..	119	Fasting
11/5/31...	140	Fasting
11/6/31.....	129	Fasting
11/7/31..	116	Fasting
11/9/31.............	99	Fasting

entirely normal in gross appearance, and palpation failed to reveal any other similar nodules. Examination of the adjacent viscera disclosed no evidence of metastases. The cystic nodule was then carefully shelled out of the pancreas by blunt dissection. The embedded surface did not appear to be well encapsulated and a small portion of the surrounding pancreatic tissue was removed with the specimen.

The patient remained rational and cooperative during the course of the operation. A specimen of blood withdrawn immediately postoperatively showed a blood sugar of 99 mg. per hundred cubic centimeters. The patient was then given an additional 25 Gm. of dextrose intravenously, the last required during the forty days that he remained in the hospital.

Postoperatively, he was placed on the usual liquid diet, without any additional carbohydrates. Blood sugar estimations during fasting were made daily for the first week. These showed values ranging from a high of 151 on the first post-operative day to a low of 99 a week later (table 4). Thereafter blood sugar determinations were made three times a week. All of the values were found to be within normal limits. The lowest was 76 and the highest 144 mg. per hundred cubic centimeters.

Fifteen days after operation a dextrose tolerance test was done. This still showed a higher than normal rise, but a normal level was reached at the end of the second hour (table 5).

The response to 1 cc. of epinephrine hydrochloride injected subcutaneously, one month after operation, is depicted in table 6.

On the morning of December 6, the patient was placed on the measured 1,800 calorie diet on which he had gone into hypoglycemic coma at six to eight hour intervals prior to the removal of the adenoma. During the ensuing week no signs or symptoms of hypoglycemia became manifest. The daily blood sugar values

TABLE 5.—*First Postoperative Dextrose Tolerance Test*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
7:15 a.m. .... 25 Gm. dextrose intravenously	91.0	Fasting
7:45 a.m.	251.0	
8:15 a.m.	179.0	
9:15 a.m.	49.3	
10:15 a.m.	44.1	
11:15 a.m.	65.5	

TABLE 6.—*Postoperative Epinephrine Response*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
8:30 a.m. .... 1 cc. epinephrine hydrochloride subcutaneously	102	Fasting
9:00 a.m.	135	
10:00 a.m.	95	
11:00 a.m.	90	

TABLE 7.—*Final Dextrose Tolerance Test*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
8:30 a.m. .... 25 Gm. dextrose intravenously	96	Fasting
9:30 a.m.	195	
10:30 a.m.	119	
11:40 a.m.	102	

made during fasting for this week ranged from 76 to 144. At the end of the week of restricted diet the final dextrose tolerance test was made (table 7). This represents an essentially normal response and would seem to indicate that a normal carbohydrate metabolism had finally been established.

The patient's convalescence was uneventful save for the development of a small pancreatic fistula which healed completely prior to his discharge from the hospital on December 12, forty days after excision of the pancreatic tumor. He has remained well and symptom-free during the ten months that have elapsed since his release. There is no external evidence of recurrence and he has been free from seizures.

Pathologic Report.—The specimen consisted of a globular mass of tissue 2 cc. in diameter which weighed about 4 Gm. The surface was irregular and presented

as a slightly lobulated, yellowish-gray, soft tissue resembling the acinous tissue of the pancreas. At one place, over an area about 5 mm. in diameter, this yellowish tissue was absent, and through this capsule there was seen a grayish-white tissue. On section, contained within the pancreatic tissue was a fairly circumscribed nodule about 1.5 cm. in diameter which was made up of a uniform grayish pink, smooth, moist, somewhat translucent tissue. The stroma appeared to be scant. There was no well defined capsule. In places the tumor tissue blended with the pancreatic tissue.

Microscopically, the tumor was made up of round and polygonal cells with eosinophilic, faintly granular-staining cytoplasm and round vesicular nuclei with
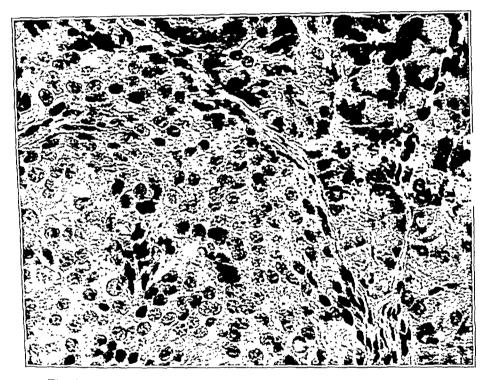
Fig. 1.—The round and polygonal cells of the tumor, separated by thin connective tissue septums, are shown.

prominent nucleoli (fig. 1). The cells grew in compact masses broken up into small alveolar formations by thin vascular connective tissue septums. In places there were wide bands of fibrous tissue interspersed between these alveolar formations, suggesting fibrous replacement of the tumor. In several sections the tumor tissue reached to the free surface where it was seen infiltrating the adjacent fatty tissue. In some areas the tumor cells surrounded small bits of the normal acinous tissue of the pancreas. In other areas there was a suggestion of invasion of the normal pancreatic tissue (fig. 2). The acinous tissue and islands of the pancreatic tissue appeared normal (fig. 3).

The special stains showed the tumor to be made up of uniformly staining cells, chiefly chromophobe, suggesting the alpha type of cell according to the Bensley terminology.
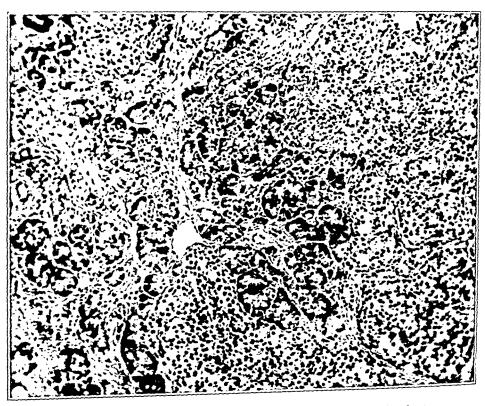
Fig. 2.—Area suggesting invasion of the normal acinous tissue by the tumor.
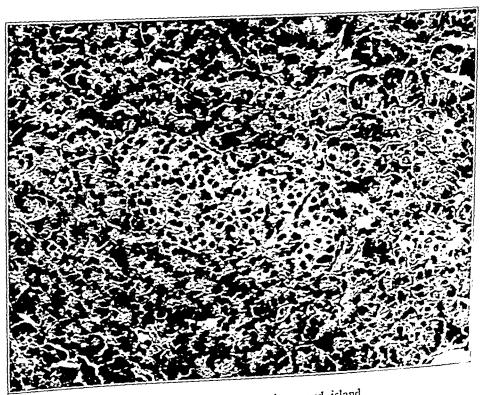
Fig. 3.—Normal acinous tissue and island.

SUMMARY

1. The history and course of a case of hyperinsulinemia with hypoglycemia secondary to a tumor involving the islands of Langerhans has been presented.

2. This case differs from the recorded cases in that the onset was apparently abrupt with complete loss of consciousness and evidence of external injury that caused his symptoms to be attributed to cerebral edema or concussion.

3. During each of his seizures of hypoglycemia, the patient presented the semi-Babinski or extensor response called to our attention by Hart and Bond as a diagnostic aid in differentiating between insulin shock and diabetic coma.

4. The complete absence of hypoglycemic seizures together with the clinical and laboratory evidence of the establishment of a normal carbohydrate metabolism immediately after the excision of the small pancreatic nodule, is, we believe, adequate proof that this man's symptoms were due to the excessive production of insulin by the tumor tissue.

5. The data here presented, together with the clinical and experimental evidence cited in the previously reported cases, suggest again that tumors arising from glandular tissue may in some instances retain the function of the organ or tissue from which they arose.

6. At the present time, exploration with removal of the adenoma, if demonstrable, offers the best chance of clinical cure.

PATHOGENESIS OF ACUTE PANCREATITIS
(ACUTE PANCREATIC NECROSIS)

LESTER R. DRAGSTEDT, Ph.D., M.D.

H. E. HAYMOND, M.D.

AND

JAMES C. ELLIS, M.D.

CHICAGO

INTRODUCTION

It is our purpose in the present paper to present data derived from both the experimental laboratory and the clinic, together with an analysis of a part of the accumulated literature, in an attempt to clarify further the problem of the pathogenesis of acute pancreatitis. At first glance, it might appear that some of the questions raised are of purely academic interest, but it is our hope that a careful examination of them may afford new avenues of approach to a better understanding of this difficult and highly important problem. All recent writers on the subject are agreed in deploring the present appalling mortality associated with the disease, and this fact alone should stimulate interest in all the various factors which may operate to produce it. In a recent paper, von Schmieden and Sebening (1927) quoted this pertinent question, "Warum sterben immer noch so viele Menschen an dieser plötzlichen und furchtbaren Krankheit"? (Why do so many people still die of this sudden and fearful disease?) An extensive experimental investigation has been conducted, and a great many significant clinical observations have been made. Much has been accomplished, and a fairly adequate surgical treatment has been developed. Indeed, it is possible that the limit has been reached in the way of operative procedure, and that a further lowering of the excessive mortality must come from another direction. The fact that the pancreas is an organ indispensable to life, the fact that it is situated in the upper part of the abdomen in close proximity to the extensive celiac nerve plexus, and the fact that it is in a region where the absorption of toxic chemical products occurs with unusual facility operate to limit the scope of surgical treatment.

While it is probable that edema and hemorrhage of the pancreatic parenchyma are frequent findings and may indeed represent early stages in the disease, it is the necrosis, sometimes limited but often extensive, that is the significant change. It has been clearly demonstrated by Archibald (1929) and confirmed by ourselves that the entrance of bile into the pancreatic duct may produce an immediate and intense edema, which later entirely subsides or in more severe cases is followed by cellular necrosis. This edema probably produces pain either through tension on the delicate pancreatic capsule or through mechanical injury to the nerves of the neighboring sympathetic visceral plexus. The symptoms have been fairly clearly defined by Zoepffel (1922), Archibald (1929), Stetten (1930) and others. Collapse and death do not occur unless necrosis succeeds the edema. It is likely that the hematogenous infection of the pancreas seen occasionally in acute epidemic parotitis is an acute pancreatitis with edema, but it is only rarely followed by necrosis.

It is thus probable that while edema and hyperemia may precede the necrosis in most cases, they are not necessarily followed by necrosis.

and they produce effects by a mechanism different from that by which necrosis is produced. There is no question that the vascular collapse, signs of toxemia and later death are the direct result of the necrosis of the pancreatic parenchyma. The term acute pancreatic necrosis is perhaps preferable to acute pancreatitis or acute hemorrhagic pancreatitis.

The fundamental questions we may ask ourselves are these: What causes the sudden extensive necrosis of the pancreas? How does a sudden extensive necrosis of the pancreas cause death? These questions are partly answered in the accumulated clinical literature if the data can be properly evaluated and in a somewhat more precise way by the direct controlled experiment.

ETIOLOGY OF ACUTE PANCREATIC NECROSIS

Agents which naturally come to mind, such as direct injury from trauma, interference with the blood supply to the pancreas through injury, thrombosis or embolism, and infection at least by way of the blood stream as in septicemia, pyemia or lodgment of infected emboli, can apparently account for a small minority of the total cases in which careful study has been made. It is significant, however, that undoubted cases have been reported in which each one of these factors has operated to produce an entirely characteristic picture of the disease. Likewise, it has been possible to reproduce the disease in the experimental animal by practically any method that insures a sudden and fairly extensive necrosis of the pancreatic parenchyma. These facts are of great importance when we come to consider the second question, namely, the cause of death resulting from pancreatic necrosis, but are of less significance in the present problem.

COMMON CHANNEL THEORY AND OBJECTIONS TO IT

The frequent association of acute pancreatic necrosis and biliary tract disease has been uniformly commented on. This prevailing opinion is amply supported by statistical evidence. Thus, Egdahl (1907) reported gallstones in 42 per cent of a series of cases of acute pancreatitis; von Schmieden and Sebening (1927), in 69.8 per cent, and Eliason and North (1930), in 71 per cent. One can hardly doubt that a patient with antecedent cholelithiasis and chronic cholecystitis is more liable to develop the disease than a normal person. It is of interest, therefore, to scrutinize carefully the evidence that has accumulated which may offer an explanation for this widely accepted and probably correct clinical observation. The theory most commonly advanced to account for this frequently noted association of acute pancreatic necrosis and biliary tract disease, the so-called common channel theory of Opie, asserts that the necrosis is due to the passage of bile over into the pancreatic duct.

Its possibility is absolutely dependent on an anatomic arrangement of the opening of the ducts into the diverticulum of Vater so that the lodgment of a small gallstone (Opie 1901, 1904, 1910) in the ampulla, a spasm of the sphincter of Oddi (Archibald 1918, 1919) or an acute edema of the duodenal mucosa in the region of the ampulla (Baló and Ballon, 1929) can close the natural opening of both ducts in the duodenum and convert them into a common continuous channel. The evidence on this point is somewhat conflicting. Opie (1904) reported that in 89 of 100 bodies examined, or 89 per cent, the common bile duct and the duct of Wirsung joined before they entered the duodenum at the papilla of Vater. Baldwin (1911) found that in 70 of a series of 90 cases, or 77 per cent, the ducts anastomosed before emptying into the duodenum. Mann and Giordano (1923), on the other hand, concluded that in only 3.5 per cent of cases was the anatomic arrangement of the ducts such as to permit the development of a common channel by obstruction at the papilla. Cameron and Noble (1924) reported that in 75 per cent of people a calculus lodged in the ampulla could convert both ducts into a common channel and permit a reflux of bile into the pancreas. Hozapfel (1930) reported that in 20 per cent of 50 bodies studied the ducts united and presented a common opening in the same papilla, whereas in 60 per cent they opened separately into the same papilla.

These statistical studies were all made on normal persons. It is unfortunate that we have no satisfactory data with regard to the arrangement of the ducts in patients with acute pancreatitis. It is possible or probable, according to Moynihan (1925), that a higher percentage of these would display a common channel. The meager published data seem to indicate the reverse. However, it is apparent that many cases of acute pancreatitis in which the bile and pancreatic ducts empty separately and at some distance apart in the duodenum have been described in the literature chiefly because in the experience of the author they represented exceptional instances.

The studies of Cameron and Noble (1924) were made on fresh cadavers, and the direct experiment of causing a small biliary calculus to lodge in the ampulla and then determining the patency or continuity of the bile and pancreatic ducts by making a cast of Wood's metal is convincing and should be less subject to error in interpretation than dissection observations on fixed tissues. However, even if we agree with these authors that in a majority of patients it is anatomically possible for the lodgment of a small stone to convert the common bile duct and duct of Wirsung into a common channel, it is not yet clear that bile will necessarily pass into the pancreas.

Theoretically, at least, it might seem that the direction of flow should depend on the relative pressures developed in the duct system of

each gland. Considerable effort has been expended to determine these pressures in the experimental animal. Mann and Giordano (1923) concluded that the secretory pressure of bile might reach from 350 to 375 mm. of bile, whereas the secretory pressure of the pancreatic juice did not exceed from 260 to 300 mm. of water, a finding in harmony with the observations of Herring and Simpson (1909) on the anesthetized dog. Granted that obstruction at the ampulla would not stop the secretion of either bile or pancreatic juice, and that the duct system was uniformly distensible throughout, this difference in pressure should make possible the passage of bile over into the pancreas. Considerable importance (Judd, 1921; Moynihan, 1925) has been attached to the observation of Mann and Giordano (1923) that during vomiting the pressure in the biliary tract rose to 1,000 mm. of bile, and the suggestion has been made that through such a mechanism vomiting might be thought to cause pancreatic necrosis. It is, however, altogether probable that the general increase in intra-abdominal pressure due to the vomiting would be equally transmitted to the pancreatic ducts and to the biliary channels and no transfer of fluid would occur. Harms (1927) reported that during the height of digestion in unanesthetized dogs the secretory pressure of the pancreas is higher than that of the liver, a finding which would suggest the passage of pancreatic juice over into the biliary channels rather than the reverse.

In view of these conflicting observations, we decided to make measurements of the secretory pressure of the pancreas in unanesthetized dogs provided with a special pancreatic fistula as illustrated in figure 1. Most of the previous determinations have been made on animals under general anesthesia, with a cannula tied in one of the pancreatic ducts and with the remaining ducts either patent or ligated. Both of these procedures, i. e., general anesthesia and cannulation of the ducts, have been found by Babkin greatly to decrease pancreatic secretion. In our preparation the ducts empty normally into a closed pouch of the duodenum, and the experiment may be made during and following the normal ingestion of food and accordingly under optimum physiologic conditions. The following protocol represents a typical experiment of this type.

Dog 732.—Feb. 15, 1931: A special pancreatic fistula, as illustrated in figure 1, was made in December, 1930. The condition of the animal was excellent; the fistula was water tight, and from 600 to 900 cc. of pancreatic juice was secreted in twenty-four hours. At 1 p. m., a meal of cooked meat was given. At 3 p. m., pancreatic juice flowed freely. The cannula was then connected by means of a rubber tube to a tall water manometer with an inside diameter of about 5 mm. The pressure gradually rose with the secretion of pancreatic juice until a maximum was reached. At this time the water in the manometer was raised 81 cm. at the height of inspiration and descended to 57 cm. during expiration.

These figures represent an average of the highest secretory pressures developed by this dog and are a measure of the column of water supported by the pressure in the pancreatic-duodenal sac measured from the level of the sac itself. The great variations in pressure caused by respiration should be noted. It is likely that vomiting would have produced as great a rise in pressure as was observed by Mann and Giordino in the biliary tract. It cannot be denied that a part of the pressure may be due to the secretion of succus entericus in the duodenal sac, but this occurs so slowly as compared with secretion of the pancreatic juice that we estimate it to be a minor factor. More important factors are the general intra-abdominal pressure and that due to the motility of the sac
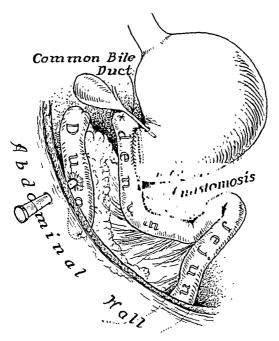
Fig. 1.—Diagrammatic illustration of the type of pancreatic fistula used. The pancreatic ducts empty into the isolated closed segment of the upper duodenum, and an external fistula has been made of this pancreatic duodenal pouch with a special gold plated cannula.

itself. For these reasons, it seems likely that the lower figure (57 cm. of water) obtained after an hour of secretion represents the secretory pressure of the gland, while the higher figures are due to extraneous factors.

It will be noted that this pressure is higher than that obtained by Mann and Giordano (1923) for the secretory pressure of bile, and supports the observation of Harms (1927). It seems to us, however, that these pressures are not the factors which alone determine the direction of flow when the duct systems of the liver and pancreas are converted

into a common channel. Of greater importance is probably the patency of the accessory pancreatic duct of Santorini, and the freedom of anastomoses between it and the branches of the duct of Wirsung within the gland. Granted a free anastomosis between the ducts and a patent duct of Santorini, obstruction at the ampulla might readily reverse the flow in the duct of Wirsung. The secretory pressure of the pancreas would, under these conditions, be ineffectual, and bile might readily pass over into the duct of Wirsung, through the anastomosing channels, and eventually reach the duodenum by way of the duct of Santorini. In cases in which the duct of Santorini is not open or in which there are insufficient anastomoses between the branches of the pancreatic ducts, we should expect from our measurements and those of Harms (1927) to find pancreatic juice passing over into the biliary channels in the event of the production of a common channel at the ampulla. In an examination of 76 specimens of adult human pancreases, Baldwin (1911) found a demonstrable anastomosis between the main and accessory pancreatic ducts within the gland in 66 cases, or 87 per cent. Opie (1904) concluded that such an anastomosis was present in nine tenths of all cases, although in many of these the union was effected by such a minute branch that one duct could not act as an outlet for the secretion of the other. If these conclusions are valid, one can readily understand the passage of bile over into the pancreatic ducts in the majority of patients in whom a common channel is established, whereas in the minority pancreatic juice may pass over into the biliary channels and possibly excite the series of pathologic changes obtained by Wolfer (1931) in the experimental animal. The cases in which pancreatic juice has been found to pass over into the common bile duct or gallbladder and escape in large quantities from a drainage tube placed in the gallbladder or common bile duct after choledochostomy for stone are instructive in this connection. Walters and Marshall (1930) cited a number of such cases and reviewed the literature. It is possible that these instances represent cases in which a common channel has been established and the direction of flow of the secretion determined by the reduction of pressure in the biliary channels artificially produced by the drainage tube. Conversely, it may be argued that a reduction of pressure in the pancreatic ducts occasioned by the anastomoses between the ducts of Wirsung and Santorini might be expected to facilitate the flow of bile over into the pancreas.

Several attempts have been made in the experimental animal to determine the direction of flow of bile when a common channel has been purposely produced. Mann and Giordano (1923) found that in the goat under these conditions bile passed readily over into the pancreas. an observation that we have recently confirmed. Wangensteen, Leven and Manson (1931) produced a common channel in cats and secured the

passage of bile over into the pancreas, particularly after the animals had been given a meal of fat, an observation which suggests that in this animal at least contraction of the gallbladder may be a real factor in determining the biliary pressure. In the dog, the major pancreatic duct empties into the duodenum at a considerable distance from the orifice of the common bile duct, and probably for this reason few attempts have been made to determine the effect of producing a common channel in this animal. We tried to produce such a condition in two dogs by making an anastomosis between the distal ends of the two ducts by means of sutures but failed to secure a patent channel. In 8 dogs a common channel was effected by means of a catheter tied securely into the ends of the common bile duct and major pancreatic duct, respectively. Five of these dogs died in from twenty-two to one hundred and thirty-two hours. Autopsy revealed a generalized peritonitis due to the escape of bile from loosening of the ligature about the bile duct (Andrews, Rewbridge and Hrdina, 1931). In no case was there evidence of bile within the pancreatic ducts. The remaining 3 dogs were killed after thirty-six, fifty-one and fifty-three days, respectively. In 2 of these the bile duct had become reestablished, while in the third it was completely obstructed. The pancreas was normal and entirely free from bile. Wolfer (1931), however, was more successful in experiments of a similar nature performed before those previously detailed were undertaken, and his results seem to indicate that when a common channel is experimentally produced in the dog by intubation of the respective ducts, pancreatic juice usually passes over into the biliary ducts rather than the reverse. The frequency of intraglandular anastomoses between the major and minor pancreatic ducts in the dog is not definitely established. In a few observations we were unable to demonstrate such anastomoses by injecting india ink into the major duct under considerable pressure. The region supplied by the minor duct did not become discolored. As previously noted, it is probable that this absence of anastomoses is significant in determining the direction of bile flow.

Direct evidence with respect to the direction of flow of the secretions in man is practically limited to autopsy observations in cases in which a gallstone has become impacted in the ampulla and a common channel established. To date, the published data indicate that under these conditions bile passes into the pancreatic ducts (Thayer, 1889; Opie, 1901; Fuchs, 1902; Bunting, 1906; Deaver, 1915; Rosenbach, 1918; Guleke, 1924; Grant, 1928). In these cases the staining of the pancreatic ducts by the bile pigment was responsible for the observation. Unfortunately, it is more or less difficult to test for the presence of pancreatic juice in the content of the biliary tract, and doubtless for this reason there is little or no evidence of its occurrence. The impaction of a

gallstone in the ampulla without evidence of pancreatitis has been repeatedly observed at operation. In cases in which recovery has followed removal of the stone, it is not possible to say whether or not a common channel existed.

The conversion of the bile and pancreatic ducts into a common channel in the cases in which it is anatomically possible (in 75 per cent of cases in man according to Cameron and Noble, 1924) is most readily understood when a small gallstone has become impacted in the orifice of the ampulla. A difficulty arises, however, when we come to survey the literature dealing with the occurrence of such impacted calculi in cases of acute pancreatic necrosis. In a series of 437 cases collected by Guleke (1924), a calculus obstructing the ampulla was found in only 1.4 per cent, and in the larger series of 1,278 cases surveyed by von Schmieden and Sebening (1927) a gallstone at the ampulla was recorded in only 4.4 per cent. It is accordingly evident that the production of a common channel in the manner postulated by Opie's theory has occurred in only a small number of instances in which acute pancreatitis has developed, even if we make a reasonable allowance for errors at autopsy or for passage of the stone into the duodenum or backward into the common duct, possibilities recognized by Thayer (1889) many years ago.

A possible solution for this difficulty may be found in the work of Archibald and Brow (1918) and Grant (1928), and in the observations of Baló and Ballon (1929). The former investigators raised the question as to the possibility of a spasm of the sphincter of Oddi converting the ducts in question into a common channel, and submitted evidence obtained for the most part from experiments on lower animals under anesthesia which they interpreted as supporting this view. In somewhat similar experiments, Wangensteen and his associates (1931) were unable to confirm these findings and stated that they were entirely unable to get regurgitation of bile into the pancreatic ducts of cats without organic obstruction at the ampulla. Mann and Giordano (1923) were likewise reluctant to admit the major postulates of Archibald's theory on the basis of insufficient direct evidence and their experience with the lower animals. These criticisms are to the point, but they do not, in our opinion, necessitate abandoning the view altogether, particularly since it is possible that the human biliary tract in the presence of a chronic infection may display disturbances in motility not readily reproduced in the lower animal. There is considerable clinical evidence that cardio-spasm and pylorospasm (of a degree not reproducible in animals under general anesthesia) are not infrequently seen in patients with chronic gallbladder disease, and it seems consequently reasonable that hyper-motility or spasm might likewise exist in the biliary tract itself, at least so far as its musculature is not destroyed.

Baló and Ballon (1929) submitted evidence indicating that swelling of the papilla duodenalis major in simple catarrhal jaundice may obstruct the pancreatic duct and lead to the retention of pancreatic juice. The possibility that a similar swelling may exist in some cases of chronic biliary tract disease and if sufficiently peripheral may produce a common channel might well be considered by those engaged in postmortem examinations and effort bent to obtain autopsies immediately after death in cases of acute pancreatic necrosis for definite evidence. The importance of the common channel and of the bile factor in acute pancreatitis in man can be determined only by such careful postmortem examination and by chemical tests with respect to the presence of biliary constituents in the ducts or substance of the necrotic pancreas.

RELATION OF BILE TO ACUTE PANCREATIC NECROSIS

The common channel theory as an explanation for the frequent association of chronic gallbladder disease and acute pancreatic necrosis has been brought into question by the discovery of cases in which both diseases have been present and in which the orifices of the common bile duct and the pancreatic duct have been found so far apart in the duodenum that a common channel could not have been formed. Such instances have been reported by Johnstone (1907, 4 cases) and Dardinski (1931, 2 cases) and doubtless many others. These findings, we believe should not be interpreted as disproving the truth of Opie's theory, since they prove only that it is insufficient to explain these particular cases. It becomes, however, necessary to search for other possibilities of extension to the pancreas from a diseased gallbladder. In this connection it should be recalled that acute pancreatic necrosis has occurred in persons with no disease of the biliary tract, the exciting agents having been hematogenous infection, thrombosis or embolism, trauma or other factors. It is not improbable that these factors have occasionally produced acute pancreatic necrosis in patients with gallstones without there being any relation between the two diseases. Such cases would obviously be confusing.

An alternative to the common channel theory, which conforms with the observed increased incidence of acute pancreatitis in patients with gallbladder disease, asserts that the former disturbance has its origin through the extension of infection from the wall of the gallbladder to the pancreas by way of the lymphatics. It has been supported by the work of Mangeret (1908), Deaver and Sweet (1921), Deaver and Pfeiffer (1921), Graham (1922) and Judd (1921). The beneficial results obtained in many cases of acute pancreatitis by cholecystectomy and common duct drainage without direct attack on the pancreas have been thought to support this view. This hardly follows, since drainage

of the common duct would reduce the biliary pressure and, in the event of a common channel, stop the further passage of bile into the pancreas or even make possible a drainage of the pancreatic ducts. A serious objection to the lymphatic extension theory is found in the complete failure to secure pancreatic necrosis in experimentally produced acute bacterial cholecystitis in animals (Kaufmann, 1927) and its rare occurrence in acute infections of the gallbladder in man. Both Grant (1928) and Wangensteen (1931) called attention to the relative safety of the nonoperative treatment of acute cholecystitis, and remarked that if lymphatic extension were a prominent factor it should occur in these acute cases more commonly than in the chronic infections. The validity of the theory and the proportion of cases of acute pancreatitis in which it accounts for the pathogenesis can be determined only by adequate bacteriologic examination at the operating table or in the postmortem room. Cultures of the bile, of the wall of the gallbladder, of the pancreas, and of the intervening tissues and lymph glands should be instructive. To our knowledge such studies have not been made.

The problem seems to resolve itself somewhat as follows: It is probable that approximately 60 per cent of the cases of acute pancreatic necrosis in man arise in patients with antecedent chronic disease of the bile tract. On the basis of the statistical information available, it is likely that in 10 per cent of these a common channel developed as the result of the impaction of a gallstone in the ampulla, and bile passed over into the pancreas. For the remaining 50 per cent comprised in this group, we must assume that a common channel developed as a result of spasm or swelling of the sphincter of Oddi, or else that bile played no direct rôle in the cause of the necrosis. If we assume that a common channel developed in the large majority of these as a result of abnormal motility of the sphincter, then the bile factor becomes of great importance in the pathogenesis of acute pancreatitis. If we adopt the reverse view, then we must account for the high incidence of pancreatitis in patients with gallstones on some other basis, presumably the extension of infection. As will be seen later, it has been amply demonstrated that the passage of bile over into the pancreatic ducts can produce acute pancreatic necrosis in animals, whereas it has been difficult or impossible to produce it by any type of experimental infection.

NONBILIARY CAUSES OF ACUTE PANCREATIC NECROSIS

There remains, however, a group of cases, approximately one third of the total, in which no evidence of gallbladder disease has been found. This group, together with the few cases discussed before in which the bile and pancreatic ducts were found to empty separately into the duodenum, proves that a fatal pancreatic necrosis can arise entirely independent of bile. The occurrence of typical cases of acute pancreatic

necrosis as a result of hematogenous infection of the pancreas is clearly indicated in the literature. Egdahl (1907), in a review of 105 cases of acute pancreatitis, cited 11 as a complication of mumps, 2 as occurring with typhoid fever, 2 with appendicitis, 1 with boils, 1 with malaria, 1 with syphilis, and 1 with pulmonary tuberculosis. McCrae (1925) reported acute pancreatitis as a complication of typhoid fever, scarlet fever, diphtheria and smallpox. The literature, mostly French, dealing with the incidence of acute pancreatitis as a complication of mumps, has been reviewed by Brahdy and Scheffer (1931). In 171 of 7,054 cases of mumps, the diagnosis of acute pancreatitis was made. In many of these cases the pancreatitis was mild, and it is likely that a considerable error in diagnosis must be allowed. Nevertheless, the statistics establish the fact that acute pancreatic necrosis may, under appropriate conditions, arise as a result of hematogenous infection. It is equally well established that trauma alone may cause typical pancreatic necrosis. Such cases have been reported by Lattes (1913) and by Holmes (1922). Katz and Winkler (1898) produced the disease in dogs by means of mass ligature of the blood supply and ducts and gross injury to the parenchyma, a result repeatedly confirmed by later workers. The theory that acute pancreatic necrosis may be produced by vascular injury, notably embolism or thrombosis, as advanced by Gilbert, Lepine and others is supported by the occasional occurrence of such cases in the clinic (Egdahl, 1907, 2 cases). The disease is, however, not readily produced in the lower animal by the ligation of the blood supply to the pancreas (Guleke, 1904, and our own experiments).

MECHANISM OF PRODUCTION OF ACUTE PANCREATIC NECROSIS

We have considered thus far the possible production of acute pancreatic necrosis in man by the introduction of bile into the pancreatic ducts, the extension of infection to the pancreas by way of the lymphatics, ducts or blood stream, direct trauma and vascular injury. According to the view of many students of this problem, all of these factors bring about the ultimate necrosis of the pancreas in the same manner. It is assumed that they cause the activation of the powerful proteolytic enzyme trypsin while it is still within the pancreatic substance or its ducts, and that the active trypsin then digests away the living pancreas. Sweet (1915) stated this view in dramatic fashion as follows: "There is, however, abundant evidence that this activation of pancreatic juice is not only what 'leads to autolysis of the cells,' but it is just this activated pancreatic juice which is responsible for the entire picture, canvas and frame, glass and signature, of this most acute and terrible intoxication, the whole secret of acute pancreatitis."

According to Moynihan (1925): "In acute pancreatitis, the immediate cause of the gland necrosis is the activation of the pancreatic juice by some agent or other, within the substance of the gland."

DOES INTRAGLANDULAR ACTIVATION OF TRYPSIN CAUSE ACUTE PANCREATIC NECROSIS?

It was demonstrated many years ago by Pavlov, Bayliss and Starling (1904) and others that the proteolytic enzyme of the pancreatic juice is secreted in an inactive form called trypsinogen, and that the pure juice in the duct system of the pancreas has no digestant effect on protein. Chepovalnikov (1899) showed that when this juice comes into contact with a substance, enterokinase, present in the secretion of the duodenal or jejunal mucosa, the trypsinogen becomes converted into the exceedingly active proteolytic ferment trypsin. Subsequent work by many investigators has demonstrated that a wide variety of substances in addition to enterokinase may activate trypsinogen, and indeed that it becomes active on long standing without the addition of extraneous material. The suggestion that this powerful proteolytic ferment is manufactured in an inactive form because otherwise it would cause the immediate digestion of the cell that made it is quite attractive, and it follows that its activation after the pancreatic secretion reaches the lumen of the intestine is innocuous because of a special property of the intestinal mucosa to resist digestion. A somewhat similar argument has been advanced to account for the normal failure of the stomach to digest itself. One may assume then, and this assumption has been generally made, that an activation of the trypsinogen in the pancreatic juice while it is still present in the duct system of the pancreas or in the secreting cells would result in the widespread self-digestion of the gland. Such a mechanism has appeared necessary to account for the great predominance of acute necrosis of the pancreas in comparison with other organs.

In this connection, it should be recalled that the cell membranes appear to be largely composed of lipoids rather than proteins, and it would appear more reasonable to expect destructive effects from fat-splitting enzymes than from those that digest proteins.

In such theories, moreover, there appears to be a misconception of the properties of enzymes. Apparently many writers regard the proteolytic enzymes, pepsin and trypsin, as corrosive chemical substances capable not only of producing a more or less complete disintegration of the protein molecule but of attacking living cells themselves. There is no evidence for such a view. Our knowledge in the highly complex field of enzyme chemistry is still very limited, but at the present time most investigators seem to be agreed that the enzymes are organic compounds, probably protein in nature, manufactured by living cells.

They are true catalysts in that they can only accelerate a reaction which otherwise would take place slowly, while they cannot start a reaction which otherwise would not occur. They may be compared with such an inorganic catalyst as spongy platinum which, when introduced into a mixture of oxygen and hydrogen, greatly increases the speed of combination of these elements, a reaction, however, already going on in the absence of the platinum. The proteolytic ferments merely increase the rate of hydrolysis of proteins produced either by a dilute acid of gastric juice or by the dilute alkali of the pancreatic secretion. The problem of the resistance of living tissues to either gastric or pancreatic digestion is primarily one of resistance to the toxic effect of dilute acid or alkali on protoplasm.

We have fairly direct evidence that this is the case with gastric juice. Claude Bernard (1859) reported that the leg of a living frog would be digested away if introduced into the stomach of a dog by way of a gastric fistula. In 1924, Vaughn and one of us (L. R. D.) found that the legs of living frogs would be similarly digested away if immersed in test tubes containing pure gastric juice obtained from a ᵛPavlov pouch in a dog. In some recent unpublished experiments, Matthews and one of us (L. R. D.) determined that this digestion is proportional to the concentration of free hydrochloric acid in the gastric juice and is little affected by the concentration of active pepsin. Thus, when the concentration of free hydrochloric acid in the juice was reduced below 0.15 per cent, no digestion of the exposed leg occurred, even though the pepsin concentration was 600 units. Conversely, vigorous digestion took place with a gastric juice of 0.45 per cent hydrochloric acid and only 20 units of pepsin.

The assumption that active pancreatic juice can digest living tissues finds its best support in the common observation that the discharges from high intestinal fistula usually cause extensive corrosion of the surrounding skin. Rosenbach (1911) reported hemorrhages in the tongue of a frog produced by the local injection of a solution containing apparently some active trypsin. The discovery that active pepsin was innocuous to living tissue suggested that a similar trial be made with trypsin. To our considerable surprise, however, the highly proteolytic pancreatic juice obtained from a fistula as illustrated in figure 1 had no digestant effect on the legs of living frogs. In a series of experiments, the hindlegs of living frogs were immersed in dog pancreatic juice containing a trypsin concentration in some cases as high as 1,000 units per cubic centimeter for as long as twenty-four hours without showing any gross evidence of digestion. Control experiments with pure gastric juice under the same conditions produced complete digestion of the skin and underlying muscles in from four to six hours. It would appear that active trypsin is just as powerless to attack living tissue as is active

pepsin, and, furthermore, that the amount of free alkali in pancreatic juice is far less corrosive than is the concentration of free hydrochloric acid in pure gastric juice.

It is clear that these experiments yield data concerning the resistance only of skin, fascia and muscle to the digestant action of active trypsin. In the following experiments an attempt was made to determine the resistance of the pancreas itself to such digestion. In 1924, Vaughn and one of us (L. R. D.) studied the resistance of various tissues to gastric digestion by implanting such organs as the spleen, kidney and intestinal mucosa into artificial defects made in the wall of the stomach in dogs. They observed that so long as the blood supply of the implant remained normal it was not digested away by the gastric content. In the present experiments, operations were performed on large, healthy dogs under general anesthesia and with strict aseptic precautions. A window approximately 2 by 5 cm. was made in the anterior wall of the duodenum about 5 cm. distal to the entrance of the lower pancreatic duct. The portion of the pancreas lying free in the adjacent duodenal mesentery was then carefully turned over and stitched into the defect in the duodenum (fig. 2). Great care was observed not to interfere with the blood supply to the pancreas in any of the manipulations. The procedure was by no means as difficult as anticipated. Pancreatic juice entering the duodenum and becoming activated on passing over the duodenal mucosa had then free access to the pancreas implant. It was appreciated, of course, that the capsule of the pancreas rather than the parenchyma would first come into contact with the active trypsin. When it was shortly found that this did not result in necrosis or digestion of the exposed pancreas, similar implants from which the capsule had been first removed and the parenchyma bared by deep grooves were exposed to the digestant action of the duodenal secretions. In neither case did digestion of the pancreas occur, although it was left exposed for periods of from several days to three months. In the latter case the duodenal mucosa had regenerated and more or less completely covered the defect. In three experiments the pancreas was implanted into a window made in the anterior wall of the stomach. The results here substantiate those found by Vaughn and one of us (L. R. D.) with the spleen and kidney. The exposed pancreatic parenchyma was not digested away by the gastric content. Microscopic sections displaying areas of the pancreas exposed to the digestant action of duodenal and gastric content respectively are shown in figures 3, 4, 5 and 6.

It seems clear that in the dog at least the active proteolytic enzymes present in the gastric or duodenal content are entirely unable to bring about necrosis or digestion of the living pancreas. A duplication of this experimental procedure is not infrequently observed in man when the floor of a large perforating gastric or duodenal ulcer is found to
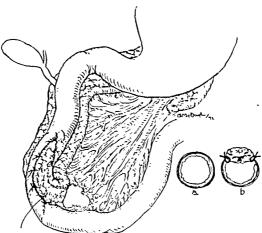
Fig. 2.—Drawing illustrating the method used to expose the living pancreas to the digestant action of the duodenal content; a shows a cross-section of the duodenum and b, a cross-section of the incised duodenum with pancreatic implant.

Fig. 3 (dog 272).—Section showing the pancreas implant in a window made in the anterior wall of the duodenum. Although exposed to the duodenal contents for eight days, there has been no digestion or evidence of necrosis of the pancreas. Regenerating duodenal epithelium may be seen extending from each side and partially covering the pancreas.

Fig. 4 (dog 108).—Section showing the pancreas implant in a window made in the anterior wall of the duodenum. Although exposed to the duodenal content for seven days there has been no digestion or evidence of necrosis of the pancreas.
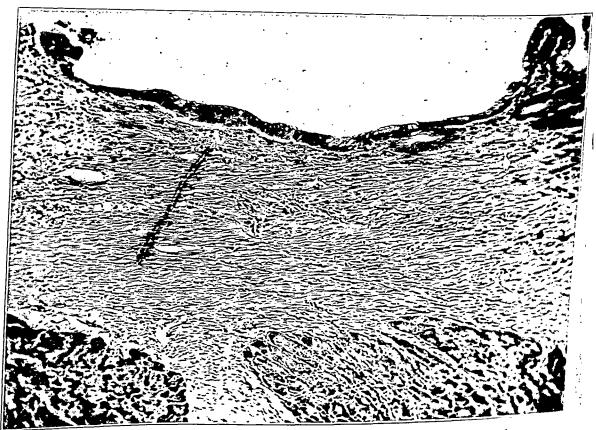
Fig. 5 (dog 108).—High power magnification of the section shown in figure 4. The regenerating duodenal epithelium is clearly seen, as well as the absence of evidence of digestion or necrosis of the pancreas implant.

consist partly or entirely of the pancreas. In the great majority of these cases digestion and necrosis of the exposed pancreas have not occurred. Exceptional instances in which an acute pancreatic necrosis has arisen as a result of a perforating gastric or duodenal ulcer have been reported by Bartels (1909) and Brocq (1919). Pearce (1904) reported a case in which a sinus from the stomach permitted intimate contact of the gastric juice with the pancreatic parenchyma, but it failed to cause acute pancreatitis.
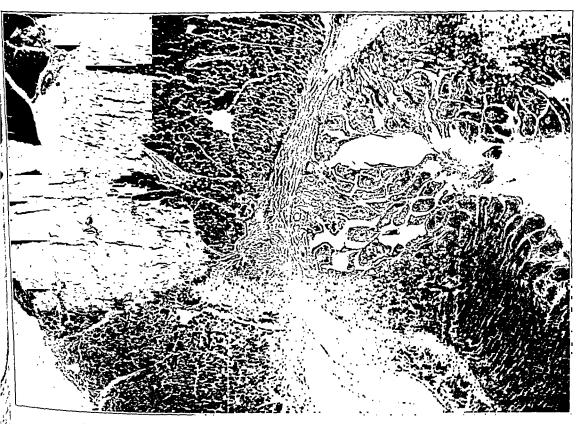
Fig. 6 (dog 734).—Section showing the pancreas implant in a window made in the anterior wall of the stomach. Although exposed to the gastric content for forty days, there has been no evidence of digestion or necrosis of the pancreas. The regenerating gastric mucosa has completely covered the implant.

The experiments with the pancreas implants in the duodenum and stomach and the instances in which a perforating ulcer has laid bare the underlying pancreas are subject to the criticism that in these cases the pancreas has been exposed, not to pure active pancreatic juice, but to the gastric or duodenal content. In the latter case it is likely that the alkalinity of the pancreatic juice has been partially reduced or neutralized by the acid of the gastric secretion and the activity of the tryptic

proteinase reduced by the accumulation of end-products of tryptic digestion. That this criticism is valid was recently illustrated in some unpublished experiments of Matthews and one of us (L. R. D.). Organs such as the spleen and kidney, which are unaffected by exposure to the gastric content, are digested away if implanted in the wall of a large Pavlov pouch, where they come into contact with pure gastric juice. In the following experiments an attempt was made to determine the effect of exposing the living pancreas of a dog to the digestant action of pure activated pancreatic juice. Animals were anesthetized by the oral administration of barbital, and the pancreas was exposed by a right rectus incision. The portion of the pancreas lying free in the duodenal mesentery was isolated by ligating and dividing a few small veins. Pure active pancreatic juice was secured from a fistula in a dog as illustrated in figure 1. About 50 cc. of this highly proteolytic secretion was placed in a small beaker, and this was then introduced into the abdominal cavity in such a way that the isolated portion of the pancreas could be entirely immersed in the pancreatic juice. The omentum and other viscera around the beaker kept the pancreatic juice at approximately body temperature. Three experiments of this type were performed. The animals were kept under complete anesthesia on the operating table until the conclusion of the experiment, when they were killed. Although continuously bathed in pancreatic juice for five, six and seven hours, respectively, in no case did the exposed area of pancreas show any evidence of digestion or necrosis in either gross or microscopic examination. These are short periods no doubt, but if the juice were markedly destructive, it would seem probable that some evidence should appear in this time.

We are well aware that in all of these trials the outer portion of the pancreatic acinus was exposed to tryptic digestion, whereas the theory postulates that it is the pancreatic juice within the ducts that, on activation, attacks the parenchyma. It is difficult to see how this could make any material difference. Many investigators have studied the effect of active trypsin within the pancreatic ducts either by the intra-ductal injection of active pancreatic juice, active trypsin solutions or substances such as succus entericus which have the property of activating trypsinogen. Roger and Garnier (1905, 1910), Falloise (1905), Carnot (1908) and Polya (1912) reported that the injection of active pancreatic juice into the pancreatic ducts of dogs produced a fatal pancreatic necrosis. According to Polya, active trypsin (a commercial preparation) was more effective in producing such necrosis than any other substance tried. When inactivated by heat, it was without effect. Williams and Busch (1907) and Mann and Giordano (1923) criticized many of these experiments on the basis that the amount of fluid injected was usually so large as to distend the finer ducts to the point of rupture

or to injure the tissue from simple mechanical distention. In an attempt to control this point, we made experiments with 3 healthy dogs each weighing approximately 7 Kg. The lower pancreatic duct in each case was isolated, and 3 cc. of active pancreatic juice obtained from a fistula, as illustrated in figure 1, was injected into the duct toward the gland and the duct subsequently severed from the duodenum and ligated. The juice used was previously determined to have a trypsin concentration of approximately 1,000 units per cubic centimeter. Studies were made of the nonprotein nitrogen, sugar and chlorides of the blood both before and after the injections. During the first twenty-four hours, the animals were considerably depressed, but no vomiting occurred. They soon regained their normal state. There were no significant alterations in the blood chemistry. All the dogs were electrocuted after fifteen days and the pancreases carefully examined. No gross or microscopic evidence of pancreatitis and no areas of fat necrosis were found.

The literature dealing with attempts to produce acute pancreatitis by the injection of substances that might be expected to activate intra-glandular trypsinogen is conflicting, and no one seems to have been very successful in producing such an acute necrosis. Eppinger (1905-1906) and Polya (1906) reported a few rather inconclusive experiments. Williams and Busch (1907) injected from 0.5 to 8 cc. of duodenal contents into the pancreatic ducts of dogs and cats. Acute pancreatitis developed in 30 per cent of these, the outcome in 2 cases being fatal. They concluded that the large amount of fluid injected ruptured the finer pancreatic ducts, for in control experiments in which similar amounts of fluid containing lampblack were injected, some of the particles were found free in the tissues. They then prepared emulsions of duodenal mucosa, sterilized by Berkefeld filtration, and injected small amounts (from 2 to 2.5 cc.) into the pancreatic ducts of 6 cats at the height of digestion, with no cases of acute pancreatitis resulting. Starling (quoted by Eve, 1915) similarly failed to produce acute pancreatitis by injecting succus entericus, sterilized by Berkefeld filtration, into the pancreatic ducts of dogs. Seemingly at variance with this experience in the laboratory have been the cases of acute pancreatitis in man in which the necrosis was limited to the portions of the gland drained by the duct of Santorini (Bassett, 1907; Johnstone, 1907; Opie and Meakins, 1909, and Simkins, 1931). These observations suggest that the etiologic agent was some material (duodenal contents) introduced into the gland via the duct. In the same category belong those cases in which an acute pancreatitis followed wide dilatation of the ducts in sloughing carcinoma of the ampulla or in which an Ascaris was found in the duct entrance (von Schmieden and Sebening, 1927). Grant (1928) called attention to the fact that the entrance of the duct of

Santorini is not protected by a sphincter, and suggested that violent vomiting may force succus entericus from the duodenum into the duct. This seems improbable since in that case we should have to assume that the general increase in intra-abdominal pressure during vomiting would be transmitted to the duodenum and not to the equally distensible pancreatic ducts. The motility of the duodenum itself is probably more effective. In this connection it should be recalled that Pearce (1904) demonstrated long ago that under normal conditions it is practically impossible to force colored liquids from the intestine of the dog into the bile or pancreatic ducts. Seidel (1910) produced a closed segment of the first part of the duodenum (the portion receiving the ducts) in dogs, and stated that the animals died in forty-eight hours with extreme hemorrhagic necrosis of the pancreas, presumably as a result of the entrance of material from the loop into the pancreatic ducts. It should be noted, however, that the production of a similar closed segment of the duodenum below the ducts will also cause death in forty-eight hours with extreme splanchnic engorgement (Whipple, Stone and Bernheim, 1913; Moorhead, Burcky and one of us [L. R. D.] 1917), and it seems probable to us that Seidel has confused this picture with acute pancreatitis. Wilkie (1921) reported a case of acute pancreatitis in a patient with duodenal dilatation, and Duval, Roux and Béclère (1928) emphasized the possibility of duodenal stasis causing a regurgitation into the duct of Santorini. Robson (1904) recognized long ago the potential danger of the damming back of infected pancreatic juice as a result of obstruction by a stone in the ampulla, a view elaborated by Nordmann (1913). Indeed, we may probably correctly assume that stasis of pancreatic juice within the dilated ducts from obstruction of any cause would in some instances be shortly followed by proliferation of bacteria in the stagnant secretion. Intestinal bacteria grow readily in pure pancreatic juice. The increased pressure within the ducts due to continued secretion and bacterial growth might well injure the walls of the duct by distention, a condition no doubt aggravated by the local toxic action of the bacteria or their products. Eve (1915) suggested that the bacteria play a double rôle: They injure the pancreatic cells by their toxins, and by their proteolytic ferments they activate the pancreatic juice, which in turn digests the damaged tissue. He quoted H. M. Vernon to the effect that various intestinal bacteria, particularly B. coli. secrete powerful proteolytic ferments which can activate trypsinogen entirely independent of enterokinase, a view shared by Mellanby and Quolley. In most cases, however, a stagnation of pancreatic juice within the ducts as a result of ligature or other obstruction produces only a gradual atrophy of the parenchyma leaving the islet tissue intact.

MECHANISM OF PRODUCTION OF PANCREATIC NECROSIS BY BILE

Claude Bernard (1856) is usually credited with being the first to produce acute pancreatitis by the injection of bile. He introduced a mixture of one part of olive oil to two parts of bile into the larger pancreatic duct of a dog and undoubtedly secured a typical and fatal pancreatitis. Subsequent work by a great number of investigators demonstrated that the injection of 5 cc. or more of gallbladder bile into the pancreatic duct and subsequent ligation will produce a fatal pancreatic necrosis in the majority of instances (Opie, 1901; Flexner and Pearce, 1901; Hewlett, 1904; Guleke, 1904; Polya, 1912, and Nordmann, 1913). The often repeated suggestion that the bile activates the trypsinogen in the duct system of the pancreas and causes necrosis in this way is probably erroneous. There is little conclusive evidence that bile activates trypsinogen, and there is no doubt about the fact that gallbladder bile produces acute pancreatitis with far greater regularity than succus entericus which contains enterokinase, the specific activator of the tryptic proteinase. It is more probable that the well known cytolytic and necrotizing properties of bile are directly responsible. It has been amply demonstrated that a wide variety of chemicals will produce pancreatic necrosis if injected into the ducts. For the most part, these have in common only the property of being locally destructive to protoplasm. The following substances have been tried and found effective: olive oil (from 5 to 8 cc.—Hess, 1903; Hewlett, 1904; Guleke, 1904, 1905, 1906, 1908; Eppinger, 1905), hydrochloric acid (5 cc. of 0.5 to 2 per cent solution—Flexner and Pearce, 1901; Hewlett, 1904), sulphuric acid (Flexner and Pearce, 1901), nitric acid (Flexner and Pearce, 1901), formaldehyde (Flexner and Pearce, 1901), zinc chloride (Lattes, 1913), chromic acid (Lattes, 1913) and calcium chloride (Binet and Brocq, 1920). It is probable that olive oil owes its activity to the liberation of highly irritating fatty acids and the formation of toxic soaps. Hess (1903) produced pancreatic necrosis by injecting from 5 to 7 cc. of oleic acid into the pancreatic ducts, and Trevor (1904) secured a similar result with a mixture of oleic acid and 4 per cent sodium soap solution. Sailer and Speese (1908) suggested that this great variety of substances that cause pancreatic necrosis on injection into the ducts is proof that it is mechanical distention of the pancreatic tissue that is the destructive agent. This objection does not appear to be valid in view of the many reports that the injection of equal amounts of bland substances does not produce necrosis. The following substances have been injected into the ducts without harmful effect: blood (Flexner and Pearce, 1901; Guleke, 1904-1908), blood serum (Flexner and Pearce, 1901), glycerin (Hess, 1903), paraffin (Hess, 1903), agar-agar (Lattes, 1913) and starch (Hess, 1903).

A fairly extensive literature exists with respect to the local and systemic toxic properties of bile and certain of its constituents. Rywosch (1901) seems to have been the first to demonstrate the toxic effect of bile on cells and its hemolyzing effect on red blood corpuscles. His results were confirmed by Flexner (1906), Meltzer and Salant (1906) and many others. Meltzer and Salant made detailed studies on the toxicity of bile and bile salts and listed an extensive bibliography. They appreciated the fact that bile salts would cause a local necrosis on contact with living cells. Bunting and Brown (1911) injected from 0.5 to 1 cc. of gallbladder bile into the peritoneal cavity of rabbits and found that the great majority died within eighteen hours. These findings were confirmed by Horrall (1929) on the dog. In one experiment we exposed the pancreas to direct contact with gallbladder bile by the following method: A dog was operated on under general anesthesia and with the usual aseptic precautions. A window was made in the gallbladder approximately 3 by 1.5 cm. in size, and the free portion of the pancreas was carefully stitched into the defect. The animal recovered from the immediate effects of the operation but died in depression fifty hours later. Autopsy disclosed an acute necrosis of the portion of the pancreas exposed to the bile. There was no evidence of peritonitis nor was there any bile in the peritoneal cavity. Flexner (1906) clearly demonstrated that the bile salts constitute the toxic element in bile and that the remaining fractions are not only not injurious but actually inhibit the destructive action of the salts. For this reason we should expect gallbladder bile, in which the bile salts are relatively concentrated, to be more toxic than hepatic duct bile. Most of the investigators previously mentioned produced pancreatic necrosis with gallbladder bile. Sodium taurocholate and sodium glycocholate are apparently equally toxic (Sellards, 1908). The suggestion of Tatum (1916) that the cytolytic action of bile is due to its activating the intracellular autolytic enzymes and that the process is essentially an autolysis of the cells was questioned by Bradley and Taylor (1917). The latter workers found that bile did not accelerate the autolysis of liver, spleen, kidney, thymus or heart muscle to any significant degree. They sharply distinguished between cytolysis and autolysis and concluded that bile does not activate the enzymes associated with autolysis. Andrews, Rewbridge and Hrdina (1931) recently confirmed the observations of Bunting and Brown (1911) and Horrall (1929) and, in addition, demonstrated that hemorrhagic peritonitis produced by the escape of bile or the injection of sterile bile salts into the peritoneal cavity is regularly associated with the invasion of B. welchii and similar organisms presumably from the intestinal tract. It is probable that the systemic intoxication in this so-called "bile peritonitis" is at least partly due to the toxins of B. welchii, although direct proof for

this statement is still lacking. In 1929, Spurrier and one of us (L. R. D.) demonstrated that bile alone can produce a fatal systemic intoxication. These investigators found that if the common bile duct of dogs was anastomosed to the vena cava or portal vein so that all of the bile passed directly back into the circulation, death regularly followed within two or three days. Sellards (1909) injected 3 cc. of a solution (2, 5 and 13 per cent strength) of sodium taurocholate into the ducts of the parotid and submaxillary glands and secured a fairly extensive necrosis of the secreting parenchyma. Andrews (1931) produced extensive necrosis of muscle and subcutaneous tissue by the injection of sterile bile or solutions of bile salts. We have confirmed the observations of Sellards and in addition have injected sterile gallbladder bile into the pelvis of the dog's kidney, followed by ligation of the ureter. In 3 healthy dogs bile was secured from the gallbladder, and 2, 6 and 8 cc., respectively, were injected into the right ureter toward the kidney. These animals were killed after twenty-four hours, and the kidneys examined both grossly and under the microscope. The pelvis of the kidney receiving 8 cc. of bile was filled with blood, and there were definite areas of necrosis and hemorrhage throughout the renal substance. The smaller amounts of bile produced mostly edema, round cell infiltration and a moderate amount of hemorrhage. In no case could the extent of the pathologic change be compared with that resulting from the injection of a like amount of bile into the pancreatic duct. Sellards (1909) similarly concluded that the lesions produced in the salivary glands by the injection of bile were less marked although similar in character to those developing in the pancreas.

There seems to be little doubt but that the pancreas is more susceptible to the local necrotizing effect of bile or bile salts than most other tissues, a conclusion voiced by Bunting and Brown (1911). It is probable that this increased susceptibility is in some way dependent on the fact that the pancreas manufactures such an active digestive secretion and one which can digest all three classes of food substances. It has been commonly remarked that acute pancreatitis is especially prone to occur immediately after a heavy meal. Many investigators have concluded that the incidence of fatal pancreatic necrosis following the intraductal injection of bile, bile salts or even other irritants is much increased if these injections are made during the height of digestion or when the pancreas has been excited by the injection of pilocarpine (Hess, 1903; Doberauer, 1906; Polya, 1912; Brocq and Morel, 1919; Wangensteen, Leven and Manson, 1931). These findings have led many naturally to conclude that the destructive agent is one of the enzymes (usually trypsin) manufactured during such periods of activity, a view we believe to be untenable. There is, however, evidence which indicates that the toxic effect of bile and perhaps of other chemicals is increased

by the presence of an active proteolytic agent. Flexner (1908) found that the mucus in bile, as well as certain other colloidal substances, limited the destructive effect of bile salts. He concluded that this was due to a lessening of the diffusibility of bile salts by the larger colloidal particles, an explanation suggested by Ostwald. Sellards (1908, 1909) reported that normal serum protects effectively against the hemolytic action of bile, a fact previously demonstrated by Bayer (1907). Bayer also showed that the inhibitory agent in the serum rests largely, if not entirely, in the protein constituents. Only the proteins of serum were found to be protective, edestin and egg albumin being without effect. Digestion of the serum by trypsin or pepsin completely destroys its protective capacity. Do we not have here a possible explanation for the extensive necrosis produced by the injection of bile into the ducts of the actively secreting pancreas? May we not assume that the initial attack of the bile has been repulsed by an exudate of serum or even frank hemorrhage? The protecting colloids being dead, proteins are then promptly digested by the tryptic proteinase and polypeptidase of the pancreatic juice and the bile salts freed for further destructive action.

SUMMARY

In considering the etiology of acute pancreatic necrosis, it should be kept in mind that it is by no means necessary to determine a single cause for all cases in order to satisfy the existing evidence with regard to its pathogenesis. Thus, the discovery of a case of acute pancreatitis in which the bile duct and pancreatic duct empty separately into the duodenum cannot be construed as evidence against the theory of Opie, but only that it is inadequate in the particular case, which may have been due to trauma, hematogenous, lymphogenous or ductal infection, or vascular injury. On the basis of the evidence existing at present, it seems probable to us that approximately 60 per cent of the cases of acute pancreatitis occurring in man have developed as a direct result of the passage of bile over into the pancreatic ducts. Included in this group are a majority of those in which an antecedent cholelithiasis and cholecystitis have existed. In making this statement, we realize that, according to the available statistical evidence, in only one sixth of this number has a common channel due to obstruction at the papilla of Vater by a gallstone been demonstrated. It is necessary, then, to believe that in the remaining five sixths of this group a common channel has been produced either by spasm of the sphincter of Oddi, transitory stone obstruction or edema of the muocsa at the papilla. No direct evidence exists to support this belief, and it does not seem likely that it will soon appear. Perhaps the most that can be said is that its possibility has been demonstrated by Archibald in experiments on lower animals, and the inescapable fact that it is easier to produce acute

pancreatic necrosis by the injection of bile into the pancreatic ducts than by any other method based on pathologic events likely to occur in man. Bile seems to produce its effect through the local toxic and cytolytic properties of the bile salts, and its action is greatly facilitated by the proteolytic enzymes of the pancreatic juice which digest and remove the protective proteins of the blood serum. Infected bile should be more effective than sterile bile, since the bacteria or their products may activate the trypsinogen. Gallbladder bile should be more effective than hepatic duct bile because of its greater concentration of bile salts.

Of the remaining 40 per cent of cases in which it seems that bile has played no rôle, we may list the following events as etiologic factors in the necrosis. They are given in the order of their probable occurrence as judged by clinical reports, namely: extension of infection via the lymphatics from an infected gallbladder or neighboring viscus, trauma, hematogenous infection as in mumps, stasis of pancreatic juice plus infection (Nordmann, 1913; Eve, 1915), reflux of duodenal content into the duct of Santorini or into the duct of Wirsung rendered patent by the entrance of an Ascaris (von Schmieden and Sebening) or because of destruction by a carcinoma, vascular injury as a result of thrombosis or embolism, and extension from a perforated ulcer. There is evidence indicating that these and perhaps other factors as well may produce an entirely typical necrosis and, as we shall see later, irrespective of the cause of the necrosis, the nature of the toxemia and death is probably the same.

CAUSE OF DEATH IN ACUTE PANCREATIC NECROSIS

The prevalent theories as to the cause of death in acute pancreatic necrosis uniformly assume that it is due to a toxemia in some way arising from the diseased pancreas. There is little direct evidence, however, supporting such an assumption. Sailer and Speese (1908) secured some indication that the blood from the carotid artery of dogs with acute pancreatitis was more toxic for guinea-pigs than normal blood. Speese, Sailer and Torrey (1911) found an increased globulin content of the blood in experimental pancreatitis, and suggested that the globulin or some substance adherent to it constitutes the toxic element in the disease. During the past year, M. L. Montgomery and one of us L. R. D. (1931) demonstrated, by means of cross-circulation experiments, the exceedingly rapid removal of toxic chemicals from the circulating blood. It was found, for instance, that a double lethal dose of strychnine injected intravenously was so completely removed within three minutes that the blood from the animal into which the injection was made could be transfused into the circulation of a normal animal without producing any toxic effect. It follows, then, that a failure to demonstrate toxic effects on transfusion of the blood from

an animal dying from acute pancreatic necrosis into a normal animal should not be construed as proof of the absence of a toxemia. It is unfortunate that there is no reliable way of determining the existence of a suspected toxemia, and in this case, as in many others, we must be provisionally content with more indirect evidence. This may be summarized as follows: A bacteremia has not been demonstrated in patients with acute pancreatic necrosis, and the clinical symptoms and findings are such as to suggest a toxemia rather than an infection. At death, a necrotic pancreas is found in the abdominal cavity. Extracts of such a pancreas have been shown to be exceedingly toxic if injected into the abdominal cavities or into the veins of experimental animals. Surgical attempts to provide an extra-abdominal escape for the products arising from the necrotic pancreas have produced results that are favorable within the limitations of the method, itself admittedly inadequate. Chemical examination of the blood has failed to show a departure from the normal of sufficient degree to account for the lethal issue.

If it is agreed that the cause of death is the systemic absorption of poisonous materials from the necrotic pancreas, and at present the weight of evidence certainly suggests this conclusion, we may perhaps profitably inquire further into the nature of these toxic substances and their mode of origin. Some questions which naturally arise are these: 1. Are the various constituents of the pancreatic juice toxic if absorbed from the peritoneal cavity? 2. Are the products of the autolysis or digestion of the pancreas by activated pancreatic juice the responsible toxic agents? 3. Are these poisonous substances bacterial toxins or toxic fractions resulting from the presence of bacteria in an extensive area of dead tissue?

OBSERVATIONS ON THE TOXICITY OF PANCREATIC JUICE

As noted in a preceding section, it has been repeatedly observed that pancreatic necrosis may occur shortly after a heavy meal at a time when presumably the pancreas is actively manufacturing its secretion. Similarly, injuries to the pancreas during digestion are apt to be more serious than during the fasting state. Attempts to induce acute necrosis by the injection of bile or other irritants into the pancreatic ducts are reported to be more successful if the gland has been previously stimulated either by taking of food or by the administration of drugs such as pilocarpine (Hess, 1903; Doberauer, 1906; Polya, 1912; Brocq and Morel, 1919; Wangensteen, Leven and Manson, 1931). These observations have usually been interpreted to indicate that the toxic agent in pancreatitis is manufactured with the pancreatic juice. Guleke (1905-1906) concluded that trypsin was the responsible toxic substance, a view shared by Sweet (1915) and many others.

The data on the toxicity of pure, or inactive, and of activated pancreatic juice are somewhat conflicting. Lattes (1913) cited the following experimenters as having demonstrated that the injection of pancreatic juice mixed with intestinal juice into a peritoneal cavity or into a vein produces a severe toxemia and death, while the injection of inactive pancreatic juice produces no such effect: Lombroso (1903), Roger and Garnier (1905, 1908), Falloise (1907), Cybulski and Tartschanow (1907), Fleig (1908), Seidel (1909) and Kircheim (1911). On the other hand, Schittenhelm and Weichardt (1911) and Stradiotti (1909) reported that the injection of large amounts of pancreatic juice either into a vein or into the abdominal cavity produced no ill effects. Lattes (1913) criticized the experiments of the latter authors in that the digestive activity of the juice was not carefully controlled. He secured juice from a cannula tied in the pancreatic duct of a dog. This was found to be without digestant effect on coagulated egg-white but had a moderate fat-splitting activity. The injection of from 7 to 103 cc. of this pure nonproteolytic juice into the abdominal cavities of dogs caused widespread fat necrosis but no toxemia, and the animals survived. Activated pancreatic juice was secured from a dog provided with a fistula of the Pavlov type, in which the duodenal mucosa containing the entrance of the lower pancreatic duct had been implanted in the skin of the abdominal wall. This juice was found to digest egg-white and to split neutral fat. The intraperitoneal injection of from 25 to 30 cc. of this secretion caused death in from nine to thirty hours (experiments on 4 dogs).

Flexner (1897) credited Senn with having been the first to demonstrate that the passage of fresh or inactive pancreatic juice (as from a cut gland) into the peritoneal cavity does not cause diffuse inflammation or marked toxemia. In 6 dogs, Lattes freed and cut the pancreatic duct, permitting the pancreatic juice to flow freely into the peritoneal cavity. He concluded that this was innocuous whether done during digestion or in the course of long periods of fasting and attributed the absence of toxicity to the lack of proteolytic activity of the fresh juice. Similar experiments in which from 5 to 20 cc. of intestinal juice was injected into the peritoneal cavity to activate the escaping pancreatic juice caused death in from ten to twenty-eight hours. The intestinal juice alone, in amounts of from 2 to 14 cc., was found to be nontoxic on intraperitoneal injection. The latter experiments are in harmony with an earlier observation of Guleke (1908), who established an intraperitoneal fistula of the pancreatic duct, securing active juice by excision of the duodenal papilla which remained attached to the duct. Death occurred six days later, at which time 400 cc. of clear bloody fluid was found in the abdomen together with numerous areas of fat necrosis. Sweet (1915) confirmed the findings of Lattes and Guleke,

and concluded that the intravenous injection of inactive pancreatic juice produced only slight transitory lowering of the blood pressure, whereas the injection of pancreatic juice plus *succus entericus*, either into the peritoneal cavity or into a vein, caused the typical symptoms of pancreatic poisoning and death. Peterson, Jobling and Eggstein (1916), on the other hand, concluded that the serum changes observed during acute experimental pancreatitis were those of an intoxication from protein split products rather than from pure tryptic ferment. There was no increase in serum protease, as would be expected from pure trypsin shock.

In view of the crucial importance of this question and the conflicting reports of various observers, we have performed a number of experiments chiefly with the view of determining, if possible, the toxicity of activated pancreatic juice. As previously noted, most investigators have agreed that the inactive juice as it exists in the duct system of the pancreas is nontoxic either on intravenous or on intraperitoneal injection. Our experiments on this point have been limited to the production of an intraperitoneal fistula of the pancreatic duct. In 5 dogs the lower or main pancreatic duct was carefully dissected free from its entrance in the duodenal wall, the duct sectioned and the duodenal end closed. In 3 cases a small ureteral catheter was tied into the proximal portion of the duct, and in each instance pancreatic juice was observed coming from the catheter. This secretion was allowed to flow freely into the peritoneal cavity in all 5 experiments and the abdomen was closed. No symptoms of toxemia appeared. The animals were subsequently killed at intervals varying from five to sixty days, and at autopsy there was surprisingly little evidence of pathologic change within the abdomen. A few small areas of fat necrosis were found in the region of the divided duct, and in 1 case, about 50 cc. of thin, turbid fluid in the peritoneal cavity. In this case the omentum was edematous and somewhat congested. These changes confirmed the previous observations of Lattes, and it seems fair to conclude, therefore, that the volume of inactive pancreatic juice which escapes from such a fistula in the dog is insufficient to produce toxemia when poured out into the peritoneal cavity. We have, of course, no check on the amount of juice secreted in these experiments, but in control experiments in which the catheter was led to the outside through a stab wound in the abdominal wall the volume obtained from the lower pancreatic duct of the dog varied from 80 to 350 cc. per twenty-four hours.

The more debated question is that with respect to the toxicity of pancreatic juice after the trypsinogen has been changed to the active trypsin. It should be recalled here that the so-called inactive pancreatic juice contains an active starch-splitting enzyme, amylopsin, and also an active lipase, steapsin. It seems somewhat surprising that the activation

of the third enzyme should convert a nontoxic fluid into one so poisonous that the intraperitoneal injection of only 25 cc. (Lattes) would produce a fatal toxemia. It may be argued, however, that trypsin attacks the protein of the cell, the basic substance of protoplasm, while the other enzymes affect only storage products such as glycogen and neutral fat. Or it may be that the reported toxicity of trypsin is independent of its catalytic action, and the mere activation of trypsinogen changes it to a general protoplasmic poison. These possibilities have seemed to us unlikely on theoretical grounds, and we have accordingly attempted to determine anew the toxicity of active (protein-digesting) pancreatic juice.

Under normal conditions, trypsinogen is activated through its contact with the succus entericus when the pancreatic juice flows over the duodenal mucosa. As previously noted, Lattes found that fresh succus entericus obtained from a Vella fistula was nontoxic on intraperitoneal injection in amounts of from 2 to 14 cc. This observation was confirmed in 1917 by Moorhead, Burcky and one of us (L. R. D.), who reported that the fresh secretions of the duodenum, jejunum and ileum, when freed from bacterial contamination, were nontoxic when allowed to drain freely into the peritoneal cavity. If, however, these secretions were kept free from preservatives and unheated, they rapidly became exceedingly toxic (Davis and Stone, 1917), presumably as a result of the accumulation of the end-products of bacterial metabolism. The necessity of determining the toxicity of mixtures of pancreatic juice and succus entericus in the complete absence of bacterial contamination was thus evident. An attempt was made to achieve this by a combination of the intraperitoneal fistula of the pancreatic duct as in Lattes' experiment and the method used by Moorhead, Burcky and one of us (L. R. D.) to test the toxicity of intestinal juice. Eight dogs were operated on in the following manner, strict aseptic precautions and general anesthesia being employed. At a point approximately 50 cm. distal to the pylorus, the jejunum was cut across in two places about 5 cm. apart. Care was taken to preserve the mesenteric blood supply to the short segment of intestine thus produced, and its mucosa was everted by a longitudinal incision along the antimesenteric border. The continuity of the intestine was reestablished by an anastomosis between the proximal and the distal jejunum. The abdomen was then closed, leaving the everted patch of jejunum to pour its secretions freely into the peritoneal cavity. One of the 8 dogs died of generalized peritonitis, but the remaining 7 showed no ill effect from the escape of succus entericus into the abdominal cavity. A second operation was done from two to three weeks later. At this time the lower pancreatic duct was isolated and cut. the duodenal end closed, and a catheter tied into the proximal end. The distal end of the catheter was sutured to the flap

of everted jejunal mucosa so that the outflowing pancreatic juice would pour over its surface and become activated before escaping into the peritoneal cavity (fig. 7). Of these 7 animals, 1 died from the anesthetic; 1 died from evisceration in sixty hours, and 3 died in twenty, forty-six and seventy hours, respectively, autopsy showing generalized peritonitis and extensive fat necrosis. In each of these cases bacteria (streptococci, staphhylococci and B. welchii) were obtained on culture from the jejunal patch at the time of the second operation and again at autopsy. Two animals survived the second operation and displayed no subsequent ill effects. These were killed twenty-eight days later. Autopsy revealed a small amount of turbid fluid in the abdomen (20 and
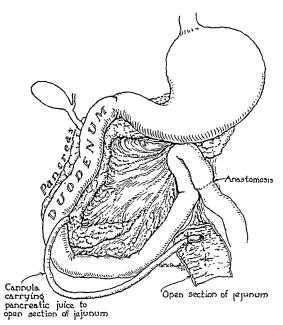
Fig. 7.—Drawing illustrating the intraperitoneal fistula of the pancreatic duct arranged so that the escaping fluid would come in contact with the mucosa of a sterile segment of the jejunum and become activated.

35 cc., respectively). The omentum was edematous and somewhat injected. No areas of fat necrosis were found. Cultures taken from the jejunal patch at the time of the second operation revealed the presence of B. welchii, streptococci and a small gram-negative bacillus.

It is difficult properly to evaluate these experiments. The three animals that died showed unmistakable evidence of a bacterial peritonitis, which might well have been the cause of death. In this case the pancreatic juice must have served as a contributing factor, since all the animals survived the production of the open section of jejunum, the source of infection. On the other hand, in the case of the 2 dogs that survived the second operation, we can hardly conclude that this proves

the nontoxicity of active pancreatic juice, since we do not know how much was poured out into the abdomen, nor have we any check on its digestive activity. In both cases pancreatic juice was observed coming from the catheter before the abdomen was closed, and it is possible that this secretion continued throughout the duration of the experiment. These strictures must apply to all similar experiments described in the literature.

In the following series of experiments active pancreatic juice was secured from the dog by means of the special type of pancreatic fistula illustrated in figure 1. The juice is, of course, activated by its contact with the duodenal mucosa lining the sac into which the cannula is fixed. Numerous determinations of the trypsin content of this product have been made by the method of Northrop and Hussey (1922-1923), and the results have shown a relatively uniform and exceedingly active secretion from day to day. With the unit of active trypsin defined by these workers, the concentration of active enzyme in 1 cc. of this pancreatic juice varies between 1,000 and 1,500 units. The activity rapidly decreases on standing at room temperature; less so if kept in the icebox. Passage through a Berkefeld filter reduces its trypsin content approximately 20 per cent. The sterile filtrate preserves its activity on standing much longer than the infected juice. The toxicity of this actively proteolytic pancreatic juice was determined by both intraperitoneal and intravenous injection into the dog and intraperitoneal injection into mice. Tests were made with the fresh juice obtained from the fistula and with the same material after filtration through a Berkefeld filter. Cultures were made to check the sterility of the filtrate. The experiments are described in the following protocols:

Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice.— Dog 306.—March 18, 1930: Fifty cubic centimeters of fresh, active pancreatic juice obtained from a pancreatic fistula and centrifugated to remove mucus and some cellular débris was injected into the peritoneal cavity. Vomiting occurred immediately. The dog was found dead twenty hours later. Autopsy revealed a small amount of bloody fluid in the abdomen, but no gross evidence of peritonitis and no fat necrosis.

Intravenous Injection of Fresh, Actively Proteolytic Pancreatic Juice.—Dog 307.—This animal weighed 12.4 Kg.; 1,070 cc. of pancreatic juice was collected from a special pancreatic fistula in twenty-four hours. The juice was centrifugated at high speed for fifteen minutes to remove suspended matter. Fifty cubic centimeters was injected intravenously. Defecation occurred immediately, and within an hour profuse salivation, vomiting and marked depression. The dog was found dead in the cage twenty hours after the injection. Autopsy revealed an extensive hemorrhagic injection of the mucosa of the duodenum, small intestine and colon. The small intestine was filled with blood and secretion.

Dog 41.—This animal weighed 9.5 Kg. One hundred cubic centimeters of fresh, active pancreatic juice from which the suspended matter had been removed by centrifugation at high speed for fifteen minutes was injected intravenously.

There was immediate defecation. In an hour a profuse bloody diarrhea developed, and the animal became markedly depressed. Death occurred four hours after the injection. There was an extensive hemorrhagic injection of the mucosa of the duodenum, small intestine and colon, and the intestines were filled with bloody mucus. Numerous small white areas were found in the pancreas. These grossly resembled areas of fat necrosis.

Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice, Sterilized by Berkefeld Filtration.—Dog 102.—Aug. 26, 1930: This animal weighed 10.6 Kg. Seventeen cubic centimeters of active pancreatic juice was collected from the fistula, immediately passed through a Berkefeld filter, and the filtrate injected into the peritoneal cavity. Cultures of the filtrate on blood agar plates, dextrose broth and litmus milk remained sterile. The milk was markedly digested by 1 drop of the juice. The dog evinced discomfort for several minutes after the injection but soon became quiet and displayed no subsequent ill effects. August 28: The dog apparently was normal. Twenty cubic centimeters of a Berkefeld filtrate of fresh, active pancreatic juice was injected into the peritoneal cavity. Cultures of the filtrate on blood agar plates and dextrose broth showed a small gram-negative bacillus. Litmus milk was markedly digested by 1 drop of the filtrate. Immediately after the injection, the dog showed discomfort and vomited repeatedly. Recovery apparently was complete. August 30: The dog apparently was normal. Thirty cubic centimeters of a Berkefeld filtrate of fresh, active pancreatic juice, collected immediately before, was injected into the peritoneal cavity. Cultures of the filtrate remained sterile. Milk was markedly digested by 1 drop of the filtrate. The animal showed signs of pain as before and vomited, but later completely recovered. September 5: The animal apparently was normal. Twenty cubic centimeters of a Berkefeld filtrate of fresh, active pancreatic juice, collected immediately before, was injected into the peritoneal cavity. Cultures of the filtrate remained sterile. Litmus milk was markedly digested by 1 drop of the filtrate. The animal displayed little or no discomfort following the injection and remained in good condition. September 8: The animal was normal. Fresh, active pancreatic juice was collected and immediately passed through a Berkefeld filter. Cultures of the filtrate remained sterile. One drop of the filtrate produced marked digestion in milk. Fifty-five cubic centimeters of the filtrate was injected into the peritoneal cavity. There was slight evidence of pain with a moderate amount of vomiting ten minutes after the injection. Complete recovery followed. September 9: The animal apparently was normal. It was electrocuted. Autopsy revealed 20 cc. of turbid fluid in the abdominal cavity, no evidence of fat necrosis, normal omentum and a peritoneum that was smooth and shining. Cultures of the peritoneal fluid remained sterile.

In this experiment a total of 142 cc. of sterile pancreatic juice, proved by its digestion of milk to be actively proteolytic, was injected into the peritoneal cavity without producing toxemia or any marked amount of fat necrosis. The last two injections seemed to produce less peritoneal irritation than those preceding. Estimations of the blood chemistry showed: on August 26, chlorides, 287; nonprotein nitrogen, 24; sugar, 108 mg.; on August 28, chlorides, 318; nonprotein nitrogen, 29; sugar, 83 mg.; on September 9, chlorides, 319; nonprotein nitrogen, 34; sugar, 132 mg. It is not probable that these variations are significant.

Dog 62.—Aug. 26, 1930: This animal weighed 9.6 Kg. Active pancreatic juice was collected, stored in the refrigerator for twelve hours, and then passed through a Berkefeld filter. Cultures of the filtrate remained sterile, and 1 drop produced marked digestion of litmus milk. Twenty-five cubic centimeters of the filtrate was injected into the peritoneal cavity. The animal was temporarily

uncomfortable but showed no subsequent ill effects. August 28: The animal was normal. Fresh, active pancreatic juice was collected and immediately passed through a Berkefeld filter. Cultures of the filtrate revealed pure growth of a small gram-negative bacillus, and 1 drop caused marked digestion of milk. Twenty-five cubic centimeters of the filtrate was injected into the peritoneal cavity. The dog vomited once ten minutes after the injection, but showed no other adverse symptoms. August 30: The animal was normal. Thirty cubic centimeters of a Berkefeld filtrate of pancreatic juice which had been proved to be sterile and actively proteolytic as in previous experiments was injected into the peritoneal cavity. The dog vomited repeatedly for thirty minutes, then recovered and remained normal. September 5: The animal was normal. Twenty cubic centimeters of a Berkefeld filtrate of fresh pancreatic juice, which had been proved to be sterile and actively proteolytic was injected into the peritoneal cavity. The dog showed little or no discomfort from the injection, did not vomit, and remained normal. September 8: The animal was normal. Forty cubic centimeters of a Berkefeld filtrate of fresh pancreatic juice which had been proved to be sterile and actively proteolytic was injected into the peritoneal cavity. The dog vomited several times and showed signs of moderate discomfort, but in twenty minutes appeared entirely normal. September 9: The animal apparently was normal. It was electrocuted. Autopsy showed within the peritoneal cavity about 100 cc. of turbid, blood-tinged fluid in which were numerous globules of fat. The omentum was edematous and slightly hemorrhagic, and careful inspection revealed numerous minute speckled areas. These areas were also observed over the small intestine and colon. The pancreas was congested and was quite firm. Cultures from the peritoneal fluid revealed an anaerobic, gas-forming, gram-positive bacillus.

In this experiment a total of 140 cc. of sterile, actively proteolytic pancreatic juice was injected into the peritoneal cavity without causing any definite evidence of toxemia. There was, however, a much greater peritoneal reaction than in the preceding experiment. The isolation of a gram-positive anaerobic bacillus from the peritoneal exudate is interesting in view of the sterility of the juice injected, except for one case in which a small gram-negative bacillus was obtained on culture. In this connection it may be recalled that Andrews and Rewbridge demonstrated the production of severe peritonitis by the intraperitoneal injection of sterile bile or sterile bile salts. At autopsy in these cases a pure culture of B. welchii was repeatedly obtained. In this experiment also the later injections of pancreatic juice produced less of peritoneal symptoms (pain and vomiting) than those preceding. Studies on the blood chemistry yielded the following results: on August 26, chlorides, 290; nonprotein nitrogen, 30; sugar, 105; on August 28, chlorides, 324; nonprotein nitrogen, 33; sugar 96; on September 9, chlorides, 303; nonprotein nitrogen, 35; sugar, 167 mg.

Dog 298.—Sept. 22, 1930: This animal weighed 8.3 Kg. Pancreatic juice was collected from the fistula and immediately passed through a Berkefeld filter. Cultures of the filter on blood agar plates, dextrose broth and a special meat medium for anaerobes gave no growth. One drop of the filtrate produced marked digestion of milk. One hundred and ten cubic centimeters of the filtrate was injected into the peritoneal cavity. The animal evinced discomfort for a few minutes after the injection, but rapidly recovered and showed no subsequent ill effects. He did not vomit. October 1: The animal apparently was normal. Eighty-five cubic centimeters of a Berkefeld filtrate of fresh pancreatic juice which had been proved to be sterile and actively proteolytic was injected into the peritoneal cavity. The dog did not vomit and apparently felt little pain. Complete recovery followed. October 3: The animal apparently was normal. It was electrocuted. Autopsy

revealed no free peritoneal fluid and no evidence of fat necrosis; the peritoneum everywhere was smooth and glistening; there was slight hyperemia of the pancreas. Determination of the blood chlorides and nonprotein nitrogen gave values within the normal range.

In this experiment large doses (85 and 110 cc.) of active pancreatic juice sterilized by Berkefeld filtration were absorbed from the peritoneal cavity without causing toxemia or fat necrosis.

Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice from the Dog into Mice.—For this experiment pancreatic juice was collected from a dog with the special pancreatic fistula previously referred to (fig. 1). The juice was used immediately after collection. In one series of mice it was injected just as it came from the fistula; in a second series, it was first centrifugated at high

TABLE 1.—*Effect of Intraperitoneal Injection of Active Pancreatic Juice (from the Dog) into Mice*

| | | | Amount | | |
Mouse	Weight, Gm.	Material Injected	Total, Cc.	Cc. per Gm.	Effect
33	31.7	Fresh active pancreatic juice of dog	0.5	0.0157	Sick; recovery in 48 hrs.
4	19.4	Fresh active pancreatic juice of dog	0.6	0.0309	Dead in 2½ hrs.
66	21.8	Fresh active pancreatic juice of dog	1.2	0.0550	Dead in 1½ hrs.
38	25.1	Fresh active pancreatic juice of dog	3.2	0.1275	Dead in 3 hrs.
41	30.2	Same as in previous experiments but centrifugated	0.5	0.0165	Sick; recovery in 48 hrs.
42	19.6	Same as in previous experiments but centrifugated	0.6	0.0306	Dead in 12 hrs.
56	26.6	Same as in previous experiments but centrifugated	1.6	0.0601	Dead in 2 hrs.
51	20.7	Same as in previous experiments but centrifugated	2.6	0.1256	Dead in 45 min.
29	36.0	Same, but passed through Berkefeld filter	0.55	0.0153	No ill effect from injection
63	31.7	Same, but passed through Berkefeld filter	1.0	0.0315	Slight depression; recovery in 1 hr.
30	20.8	Same, but passed through Berkefeld filter	1.2	0.0577	Slight depression; recovery in 1 hr.
64	26.2	Same, but passed through Berkefeld filter	3.3	0.1259	Moderate depression; recovery in 24 hrs.

speed for fifteen minutes, while in the third it was first passed through a Berkefeld filter. The data are shown in table 1. There was no difference between the centrifugated and uncentrifugated preparations. In both cases the intraperitoneal injection of as little as 0.03 cc. of juice per gram of body weight caused death. On the other hand, the Berkefeld filtrate was so little toxic that a dose four times as great produced few or no symptoms.

Comment.—The results of our experiments with respect to the toxicity of pure inactive pancreatic juice (intraductal juice) confirm those of others, and we may probably safely conclude that in the dog at least the escape of pancreatic juice from the severed duct does not produce marked toxemia and but little peritoneal reaction. The active lipase in this juice seems to be entirely unable to digest the lipoid envelop of living cells and produce necrosis. The areas of so-called

fat necrosis, so characteristic of acute pancreatitis, probably represent areas of devitalized or dead cells the fat of which on coming into contact with the steapsin of the pancreatic juice has been converted into glycerin and fatty acids, the latter combining with the ubiquitous calcium to form soap. Some such explanation seems necessary to account for the widely scattered areas of such necrosis and the intervening more accessible normal fatty tissue.

It should be emphasized that pancreatic juice obtained directly from the duct is usually sterile (Elman and McCaughan, 1927), whereas that activated by admixture with succus entericus contains the usual intestinal bacteria. The intravenous injection of this contaminated pancreatic juice was found to cause a violent toxemia, characterized by the same extreme splanchnic engorgement that is produced by the toxic proteose of Whipple, histamine or the toxic substances accumulating in isolated closed intestinal loops. On the other hand, when such activated pancreatic juice was freshly obtained from the dog and immediately passed through a Berkefeld N filter, as much as 110 cc. was injected into the peritoneal cavity of a dog weighing 8 Kg. without producing toxemia. Similar results were obtained in the experiments on mice. The contaminated pancreatic juice was found to be toxic, whereas after Berkefeld filtration, 3.3 cc. injected intraperitoneally produced only a moderate depression. Calculated by weight, this would correspond to a dose of 1,260 cc. for a dog weighing 10 Kg.

It is probable that the degree of insult to the pancreas capable of producing fatal pancreatitis causes also complete cessation of pancreatic secretion. It has been the experience of most physiologists that the pancreas is exceptionally sensitive to trauma and that even a slight disturbance may stop secretion for many hours. In assaying the part played by trypsin in the toxemia of acute pancreatic necrosis, therefore, we should probably limit ourselves to such amounts as might reasonably be presumed to exist both in the intraductal pancreatic juice and the secreting cells. We have no definite data with respect to the concentration of trypsin, or rather of its precursor, trypsinogen, in the secreting cells at any one moment, but we shall probably not err greatly if we assume it to be of the same order of magnitude as in the pancreatic juice. The pancreas of a dog weighing from 10 to 15 Kg. weighs from 30 to 35 Gm., and its autolysis within the peritoneal cavity might be expected to liberate no more trypsin than is contained in an equal weight of active pancreatic juice. The probable presence of trypsin-inhibiting substances in the autolyzing pancreas should make this estimate quite liberal.

If these strictures are valid, we must conclude that neither trypsinogen nor trypsin represents the toxic agent in this disease. Attempts such as those of von Bergmann (1906), Joseph and Prigsheim (1913),

and Ohno (1923) to produce immunity or a therapeutic serum by the injection of purified trypsin solutions, we should expect to be futile.

OBSERVATIONS ON THE TOXICITY OF END-PRODUCTS OF PANCREAS DIGESTION AND AUTOLYSIS AND THE RÔLE OF BACTERIA IN THE TOXEMIA OF ACUTE PANCREATIC NECROSIS

One of the methods frequently employed to study the toxemia of acute pancreatitis has been to remove the pancreas from one animal under strict aseptic conditions and implant it in the abdominal cavity of a second, where it is permitted to undergo self-digestion, or autolysis. Guleke (1904, 1905 and 1906) reported that when this is done profound toxemia develops in the animal receiving the pancreas implant, and death occurs in from nine to eighteen hours, a finding confirmed by many others (Maragliano, 1912; Lattes, 1913; Sweet, 1915). Death has usually been attributed to the assumed toxic properties of the pancreatic ferments or to various protein split products arising as a result of the autolysis of the gland. The successful production of a typical fatal toxemia when all extraneous bacterial contamination has been avoided has led practically all investigators to disregard the possibility of bacterial products playing a part in the disease.

A series of experiments performed by the senior author (L. R. D.) over a number of years on the nature of the toxemia in acute intestinal obstruction has led him to question seriously the probability of highly toxic products arising in the body as a result of the autolytic destruction of body protein in the absence of bacteria. It should be recalled that such autolysis is a normal physiologic process for removing dead cells and protein exudates, and that a mechanism exists for the utilization of its end-products in the metabolism of the organism. It is a common observation in pathologic processes that extensive areas of spleen, kidney, bone or muscle may undergo aseptic necrosis as a result of infarction without the production of a severe toxemia. It is possible in the dog to occlude the blood supply to the spleen, kidney or a short isolated segment of intestine, previously sterilized by prolonged drainage into the peritoneal cavity, without the development of adverse symptoms, provided bacteria do not gain access to the necrotic autolyzing tissue. In 1924, Mason, Davidson, Matthew and Rastello reported that the aseptic autolysis of portions of dog liver implanted in the abdominal cavity regularly produced a fatal toxemia. In these experiments the authors took pains to avoid bacterial contamination during the operations, but did not apparently make cultures of the normal tissue. This apparent exception led two of us to reinvestigate the question (J. C. E. and L. R. D., 1930). It was soon found that the uncontaminated hepatic tissues of normal dogs regularly contain bacteria (predomi-

nantly anaerobes resembling if not identical with B. welchii), and that the toxemia resulting from the in vivo autolysis of liver (as in the experiments of Mason and co-workers) is entirely dependent on the presence of these organisms. Presumably various highly toxic chemical fractions arise as a result of the activity of bacteria growing in a large area of dead and disintegrating tissue. These observations were soon confirmed by Dvorak (1932).

It seemed therefore advisable to determine in a similar way if bacteria are commonly present in the pancreatic tissues of healthy animals, and, if so, their relation to the toxemia resulting from autolysis of the pancreas in vivo. It seems strange, in view of the extensive bacteriologic studies of diseased tissues, that so little work has been done to determine the bacterial flora of normal organs or rather of the uncontaminated tissues of healthy living animals and man. In 1930, the

TABLE 2.—*Incidence of Bacteria in Uncontaminated Pancreatic Tissues of Healthy Living Rabbits* *

Rab-bit	Smears	Blood-Agar Plates	Lactic Acid Medium	Milk Medium
1	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
2	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
3	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
4	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
5	Gram-positive bacilli	No growth	....	Anaerobic bacillus
6	Gram-positive bacilli	Gram-negative bacilli	B. coli	No growth
7	Gram-positive bacilli	Gram-negative bacilli	B. coli	No growth
8	Gram-negative bacilli, gram-positive cocci	Staph. aureus	B. coli	No growth
9	Gram-positive bacilli	No growth	....	Anaerobic bacillus
10	Gram-negative diplococci	Staph. albus	....	Anaerobic bacillus

* The rabbits were anesthetized with ether. The abdomen was shaved and painted twice with tincture of iodine. Linen, gowns, rubber gloves and instruments were sterilized after each operation.

literature was briefly reviewed by two of us (J. C. E. and L. R. D.). The present experiments, decidedly limited in scope, have been performed merely to determine the presence of bacteria in the uncontaminated pancreatic tissues of living healthy rabbits and dogs. It is obvious that a more quantitative study is necessary as well as a more detailed investigation regarding the location of organisms in the pancreas and the relative frequency of different bacterial types. A summary of the results obtained to date is given in tables 2 and 3. It proves to our mind conclusively that bacteria are present in the pancreatic tissues of the great majority of healthy living rabbits and dogs.

The great importance of these bacteria in the toxemia resulting from in vivo autolysis of pancreas is demonstrated in the following experiments:

In Vivo Autolysis of Dog Pancreas Complicated by the Presence of Bacteria Commonly Found in the Uncontaminated Gland.—The data included in table 3 summarize the experiments with 18 dogs in which

a portion or the whole of the pancreas of a second animal has been secured with strict aseptic precautions and implanted into the abdominal cavity. Of these, 8 received one half of the pancreas from an animal

TABLE 3.—*Incidence of Bacteria in Uncontaminated Pancreatic Tissues of Healthy Living Dogs and the Relation of Bacteria to the Toxemia Arising from in Vivo Autolysis of Pancreas*

Dog	Amount of Pancreas Implanted	Cultures of Pancreas Before Implantation	Weight of Dog Receiving Implant, Kg.	Result of Implantation with Cultures of Peritoneal Exudate
986	½ of a pancreas; weight, 12 Gm. (wrapped in omentum)	Bacteria present but not identified	12.15	Dead 30 hrs.; B. welchii, streptococci and staphylococci
948	½ of a pancreas; weight, 16 Gm.	Staphylococci	6.5	Dead in 3 days; no cultures taken
949	½ of a pancreas; weight, 16 Gm.	Staphylococci	7.4	Survived; killed after 3 days; cultures lost
309	½ of a pancreas; weight, 20 Gm.	Gram-negative bipolar bacillus	6.5	Survived; killed in 11 days; staphylococci
916	½ of a pancreas; weight, 20 Gm.	Gram-negative bipolar bacillus	7.4	Survived; killed after 41 days; exudate sterile
275	½ of a pancreas; weight, 15 Gm.; cut in many fine pieces	No growth	7.7	Survived; killed after 14 days; peritoneal cavity sterile
276	½ of a pancreas; weight, 16 Gm.; cut in many fine pieces	No growth	6.4	Survived; killed after 14 days; peritoneal cavity sterile
983	½ of a pancreas; weight, 20 Gm.; triturated with 50 cc. sterile saline	Bacteria present but not identified	11.3	Survived; killed after 23 days; cultures of peritoneum revealed gram-positive bacillus and staphylococci
513	Entire pancreas; weight, 35 Gm.	No cultures taken	6.5	Dead in 18 hrs.; B. welchii in exudate
732	Entire pancreas; weight, 38 Gm.	Gram-positive anaerobic bacilli	7.5	Dead in 18 hrs.; B. welchii and gram-negative diplococci
629	Entire pancreas; weight, 34 Gm.	Gram-positive anaerobic bacilli	5.3	Dead in 24 hrs.; B. welchii and gram-positive diplococci
419	Entire pancreas; weight, 31 Gm.	Gram-positive and gram-negative anaerobic bacilli	6.0	Dead in 24 hrs.; B. welchii, streptococci, gram-negative bacilli
588	Entire pancreas; weight, 35 Gm.	Gram-positive anaerobic bacilli	6.4	Dead in 46 hrs.; B. welchii and staphylococci
636	Entire pancreas; weight, 35 Gm.	Gram-positive anaerobic bacilli	7.5	Dead in 22 hrs.; B. welchii, B. coli and staphylococci
788	Entire pancreas; weight, 30 Gm.	All cultures remained sterile	5.6	Dead in 20 hrs.; B. welchii
548	Entire pancreas; weight, 35 Gm.	All cultures remained sterile	12.0	Survived; killed after 21 days; peritoneal cavity sterile
787	Entire pancreas; weight, 35 Gm.	Gram-positive anaerobic bacilli	5.8	Survived; killed after 16 days; gram-positive anaerobic bacilli
396	Entire pancreas; weight, 32 Gm.	Gram-negative bipolar bacillus	8.0	Survived; killed after 40 days; peritoneal cavity sterile

of approximately the same weight and 10 an entire pancreas. Two of the 8 died and 6 survived. Of the 10 receiving the entire pancreas, 3 survived and 10 died.

It is apparent that under these conditions it requires the in vivo necrosis of from one-half to the whole of a pancreas regularly to cause the death of an otherwise healthy dog. It is true that the animal's own

pancreas has been undisturbed and that there is accordingly no factor of pancreatic insufficiency such as complicates the disease in man. It is, however, unlikely that this plays any part in such an acute process, since the complete removal of the pancreas in the dog is compatible with life for from five to ten days without special treatment. It is noteworthy that none of the animals died in less than eighteen hours. Apparently this much time at least is required for the production of a fatal toxemia, even in the presence of a sudden necrosis of the entire gland. Clinical reports of death within four or five hours of the onset of the disease suggest either that man is more susceptible to this type of toxemia or that other complicating factors are present. Cultures taken from the uncontaminated pancreas in 17 of these experiments revealed the presence of bacteria in all but 4, or an incidence of 76 per cent. Cultures taken from the peritoneal exudate in the immediate vicinity of the autolyzing gland in the animals that died were all positive, and it is doubtless significant that an anaerobic gram-positive bacillus resembling, if not identical with, B. welchii was obtained in each case.

In Vivo Autolysis of Fetal Pancreas.—The following experiment illustrates the innocuous effect of fetal pancreas:

A cesarean section was performed on a bitch near term and the entire pancreas from each of 4 of the fetuses secured. Careful aseptic precautions were observed, and cultures, both aerobic and anaerobic, proved the sterility of these fetal glands. The four glands were placed in the free peritoneal cavity of a dog weighing 9 Kg., and the abdomen was closed. The animal promptly recovered from the operation and displayed no subsequent ill effects. At autopsy six weeks later, no trace of the implanted tissue could be found.

Intraperitoneal Digestion of Sterile Autoclaved Pancreas.—Four experiments were performed in this group, the results of which are summarized in the following protocols:

Dog 985.—Aug. 15, 1930: This animal weighed 13.8 Kg. The abdomen was opened, and a portion of dog pancreas weighing approximately 18 Gm., which had been previously autoclaved at 15 pounds' pressure for twenty minutes, was placed in the peritoneal cavity, surrounded by omentum, and the abdomen closed. Cultures proved the implanted pancreas to be sterile. The animal promptly recovered and displayed no subsequent ill effects. The values for blood chlorides, sugar and nonprotein and urea nitrogen remained within normal range. The dog was electrocuted after twenty-one days, and autopsy revealed the implanted pancreas completely wrapped in omentum. It was somewhat reduced in amount and caseous in consistency.

Dog 991.—Aug. 15, 1930: This animal weighed 11.7 Kg. The abdomen was opened, and about 20 Gm. of fresh macerated dog pancreas was placed in the free peritoneal cavity. This pancreas had been first autoclaved at 15 pounds' pressure for fifteen minutes and found to be sterile by culture. The animal recovered promptly from the operation and continued in good health. The values *for*

blood chlorides, sugar and nonprotein and urea nitrogen remained within the normal range. The dog was electrocuted after twenty-one days, and autopsy revealed numerous caseous masses, the remains of the implanted pancreas, encapsulated in omentum.

Dog 414.—April 15, 1930: This animal weighed 6 Kg. The abdomen was opened, and about 35 Gm. of pancreas (the entire gland from a dog of somewhat larger size) was implanted in the free peritoneal cavity. This pancreas had been previously autoclaved at 15 pounds' pressure for fifteen minutes and found to be sterile by culture. The animal promptly recovered from the operation and continued in good health. The blood chemistry showed no deviation from the normal. The dog was killed after eleven days, and postmortem examination was performed immediately. The abdominal cavity was entirely normal and contained no free fluid. The implanted pancreas was still firm in consistency and about one half of its original size. It was partially encapsulated in omentum.

Dog 488.—April 15, 1930: This animal weighed 7 Kg. The abdomen was opened, and about 34 Gm. of pancreas (the entire gland from a dog considerably larger in size) was implanted in the free peritoneal cavity. This pancreas had been first autoclaved at 15 pounds' pressure for fifteen minutes and proved to be sterile by culture. The animal promptly recovered from the operation and did not display any subsequent ill effects. The blood chemistry remained within the normal range. The dog was killed after one hundred and fifty-one days, and immediate postmortem examination was performed. The peritoneal cavity was entirely normal, and no trace of the implanted pancreas could be found.

The rate of disintegration of the autoclaved pancreas placed in the abdominal cavity was obviously much slower than that of the fresh gland. This was to be expected since the heat was adequate to destroy all the pancreatic enzymes and effectually check autolysis. A complete digestion and removal of the necrotic sterile pancreas was, however, eventually brought about, presumably by ferments and cellular elements provided by the host, without the development of any symptoms of toxemia. This fact may be interpreted to indicate either that the end-products of the aseptic digestion of pancreas are not toxic, or, if they are toxic, that under these conditions they are elaborated so slowly that the defense mechanism of the body can detoxify and excrete them.

Toxicity of the End-Products of the Aseptic Digestion of Pancreas in Vitro.—Many observations have been made with respect to the end-products resulting from the autolysis, or self-digestion, of various tissues in vitro. For the most part, investigators have been interested in the chemical identification of some of the products of these digests, and determinations of their toxicity have, as a rule, not been made. The majority of such experiments, moreover, have been conducted without sufficient care to exclude bacterial contamination. Incubation between layers of toluene and chloroform has usually been adopted as a method for inhibiting bacterial growth, but adequate bacteriologic checks have rarely been made. It is clear from what has been found regarding the frequency of bacteria in the uncontaminated tissues of healthy ani-

mals that even the strictest aseptic precautions employed in removing organs cannot be relied on to exclude bacterial activity in autolysates free from antiseptics.

In the following experiments we have made an attempt to digest various sterile tissues in vitro with sterile gastric and pancreatic juice and to compare the toxicity of these digests with others containing the bacteria commonly found in the respective tissues in situ. Specimens of pancreas, liver and muscle were freshly secured and immediately autoclaved at 15 pounds' pressure for fifteen minutes. Gastric juice from an isolated stomach pouch (L. R. D. and J. C. E., 1930) and pancreatic juice from a fistula were freed from bacteria by Berkefeld filtration. The sterility of the resulting digests was checked by cultures for both aerobic and anaerobic organisms. It is probable that in acute pancreatic necrosis the responsible toxins are absorbed from the peritoneal cavity. Whether they pass directly into the capillaries draining into the portal system or into the lymphatics is unknown. It is fairly certain, however, that they must pass through a layer of endothelium before they reach the blood stream, and it is consequently probable that the injection of toxic fractions obtained from the pancreas into the peritoneal cavity more nearly reproduces the conditions of the disease studied than the injection of these fractions into a vein. In the latter case, it may be difficult to distinguish between the shock resulting from the intravenous injection of particulate matter and the toxemia of a soluble poison. For this reason the toxicity of each of these in vitro digests of pancreas, liver and muscle was determined by intraperitoneal injection. Mice were selected because the number of injections precluded the use of a larger animal. The results are summarized in table 4. To our mind, they prove conclusively that the digestion of pancreas, liver or muscle by gastric or pancreatic juice in the absence of bacterial contamination does not produce toxic end-products, whereas these develop in relatively large amount under the same conditions when the bacteria commonly found in these tissues are present.

Intraperitoneal Digestion of Autoclaved Pancreas by Sterile Pancreatic Juice.—The experiments described in the third section justify the conclusion that the end-products resulting from the digestion of the sterilized pancreas by the ferments of the peritoneal cavity are not sufficiently toxic to produce symptoms, or if toxic they are elaborated too slowly to produce toxemia. The heat of the autoclave has, of course, destroyed the pancreatic ferments, and one may reasonably raise the question: May not the digestion of sterile pancreas by the enzymes of the pancreatic juice produce different and more toxic chemical fractions than result from the slow disintegration of the autoclaved pancreas in the peritoneal cavity? It seems reasonable to infer that in clinical cases of acute pancreatic necrosis the dead cells are broken down in large

TABLE 4.—*Toxicity of the End-Products Resulting from the Aseptic Peptic and Tryptic Digestion of Pancreas, Liver and Muscle*

Mouse	Weight, Gm.	Material Injected Intraperitoneally*	Total Amount, Cc.	No. of Cc. per Gm. Body Weight	Result
1	29.5	Solution A (tryptic pancreas digest, aseptic)	1.0	0.034	No toxic effect
2	32.0	Solution A (tryptic pancreas digest, aseptic)	2.0	0.063	No toxic effect
3	30.6	Solution A (tryptic pancreas digest, aseptic)	3.0	0.098	No toxic effect
4	27.0	Solution A (tryptic pancreas digest, aseptic)	4.0	0.148	No toxic effect
5	29.0	Solution B (peptic pancreas digest, aseptic)	1.0	0.035	No toxic effect
6	32.4	Solution B (peptic pancreas digest, aseptic)	2.0	0.062	No toxic effect
7	30.5	Solution B (peptic pancreas digest, aseptic)	3.0	0.098	No toxic effect
8	19.0	Solution B (peptic pancreas digest, aseptic)	4.0	0.211	Dead in 1 hr.†
9	31.0	Solution C (pancreas autolysate, infected)	1.0	0.032	Dead in 20 hrs.
10	23.0	Solution C (pancreas autolysate, infected)	0.5	0.022	Dead in 19 hrs.
11	30.1	Solution C (pancreas autolysate, infected)	0.33	0.011	Dead in 19 hrs.
12	25.0	Solution C (pancreas autolysate, infected)	0.25	0.010	Dead in 19 hrs.
13	32.0	Solution D (tryptic pancreas digest, infected)	1.0	0.031	Dead in 20 hrs.
14	20.0	Solution D (tryptic pancreas digest, infected)	0.5	0.025	Dead in 18 hrs.
15	22.3	Solution D (tryptic pancreas digest, infected)	0.33	0.015	Survived
16	24.0	Solution D (tryptic pancreas digest, infected)	0.25	0.010	No toxic effect
17	23.0	Solution E (tryptic liver digest, aseptic)	1.0	0.043	No toxic effect
18	23.5	Solution E (tryptic liver digest, aseptic)	2.0	0.085	No toxic effect
19	26.8	Solution E (tryptic liver digest, aseptic)	3.0	0.112	No toxic effect
20	30.6	Solution E (tryptic liver digest, aseptic)	4.0	0.131	No toxic effect
21	32.0	Solution F (peptic liver digest, aseptic)	1.0	0.031	No toxic effect
22	26.4	Solution F (peptic liver digest, aseptic)	2.0	0.076	No toxic effect
23	20.2	Solution F (peptic liver digest, aseptic)	3.0	0.149	No toxic effect
24	24.0	Solution F (peptic liver digest, aseptic)	4.0	0.167	Dead in 19 hrs.
25	30.0	Solution G (liver autolysate, infected)	1.0	0.033	Dead in 20 hrs.
26	22.0	Solution G (liver autolysate, infected)	0.5	0.023	Dead in 18 hrs.
27	24.9	Solution G (liver autolysate, infected)	0.33	0.011	Dead in 3 hrs.
28	19.5	Solution G (liver autolysate, infected)	0.25	0.013	Dead in 2 hrs.
29	29.0	Solution H (tryptic liver digest, infected)	1.0	0.034	Dead in 20 hrs.
30	29.0	Solution H (tryptic liver digest, infected)	0.5	0.016	Dead in 7 hrs.
31	21.6	Solution H (tryptic liver digest, infected)	0.33	0.015	Survived
32	28.0	Solution H (tryptic liver digest, infected)	0.25	0.009	Dead in 46 hrs.
33	26.7	Solution I (tryptic muscle digest, aseptic)	1.0	0.037	No toxic effect
34	24.0	Solution I (tryptic muscle digest, aseptic)	2.0	0.083	No toxic effect
35	25.5	Solution I (tryptic muscle digest, aseptic)	3.0	0.176	No toxic effect
36	19.0	Solution I (tryptic muscle digest, aseptic)	4.0	0.211	No toxic effect
37	23.2	Solution J (peptic muscle digest, aseptic)	1.0	0.043	No toxic effect
38	25.0	Solution J (peptic muscle digest, aseptic)	2.0	0.080	No toxic effect
39	19.4	Solution J (peptic muscle digest, aseptic)	3.0	0.155	No toxic effect
40	28.4	Solution J (peptic muscle digest, aseptic)	4.0	0.141	No toxic effect
41	17.4	Solution K (muscle autolysate, infected)	1.0	0.057	Dead in 20 hrs.
42	33.0	Solution K (muscle autolysate, infected)	0.5	0.015	Survived
43	30.4	Solution K (muscle autolysate, infected)	0.33	0.011	Dead in 22 hrs.
44	22.0	Solution K (muscle autolysate, infected)	0.25	0.011	Dead in 3 hrs.
45	20.0	Solution L (tryptic muscle digest, infected)	1.0	0.050	Dead in 20 hrs.
46	23.0	Solution L (tryptic muscle digest, infected)	0.5	0.022	Dead in 18 hrs.
47	30.3	Solution L (tryptic muscle digest, infected)	0.33	0.011	Survived
48	15.0	Solution L (tryptic muscle digest, infected)	0.25	0.017	Dead in 19 hrs.

* Solution A (tryptic pancreas digest, aseptic): Ten grams of fresh dog pancreas plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of fresh dog pancreatic juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the solid material was practically all in solution. Cultures of the digest all remained sterile. Eight cubic centimeters represented 1 Gm. of pancreas. The toxicity of the mixture was determined by intraperitoneal injections in mice.

Solution B (peptic pancreas digest, aseptic): Ten grams of fresh dog pancreas plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of pure dog gastric juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the pancreas was entirely digested and in solution. Cultures of the digest all remained sterile. Eight cubic centimeters represented 1 Gm. of pancreas.

Solution C (pancreas autolysate, infected): Ten grams of fresh uncontaminated dog pancreas plus 70 cc. of sterile Ringer's solution was incubated at 37 C. for sixty-eight hours. A scum formed on the surface of the solution, and this was found to contain many gram-positive cocci and gram-positive bacilli; 0.64 Gm. of solid material remained, so that 8.5 cc. represented 1 Gm. of pancreas. The toxicity of the filtrate was determined by intraperitoneal injections in mice.

Solution D (tryptic pancreas digest, infected): Ten grams of fresh uncontaminated dog pancreas plus 20 cc. of Ringer's solution plus 50 cc. of fresh dog pancreatic juice was incubated at 37 C. for forty-two hours. There was a luxuriant growth of bacteria in the mixture (gram-negative bacilli and gram-positive cocci); 1.26 Gm. of solid material remained undigested, so that 1 cc. represented 109 mg. of pancreas.

Solution E (tryptic liver digest, aseptic): Ten grams of fresh dog liver plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of fresh dog pancreatic juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the solid material was practically all in solution. Cultures of the digest all remained sterile. One cubic centimeter represented 125 mg. of fresh liver.

Solution F (peptic liver digest, aseptic): Ten grams of fresh dog liver plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of pure dog gastric juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the solid material was practically all in solution. Cultures of the digest all remained sterile. One cubic centimeter represented 125 mg. of fresh liver.

Solution G (liver autolysate, infected): Ten grams of fresh uncontaminated dog liver plus 70 cc. of sterile Ringer's solution was incubated at 37 C. for sixty-eight hours. A scum formed on the surface of the solution, and this was found to contain many bacteria (gram-negative bacilli); 0.81 Gm. of solid material remained, so that 1 cc. represented 115 mg. of fresh liver.

Solution H (tryptic liver digest, infected): Ten grams of fresh uncontaminated dog liver plus 20 cc. of Ringer's solution plus 50 cc. of fresh dog pancreatic juice was incubated at 37 C. for forty-two hours. There was a luxuriant growth of bacteria in the mixture (gram-positive bacilli and cocci); 1.65 Gm. of solid material remained undigested, so that 1 cc. represented 104 mg. of liver.

Solution I (tryptic muscle digest, aseptic): Ten grams of fresh dog muscle plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 43 cc. of fresh dog pancreatic juice sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours at which time the muscle was entirely digested. Cultures of the digest showed a meager growth of gram-negative bacilli. One cubic centimeter represented 137 mg. of muscle.

Solution J (peptic muscle digest, aseptic): Ten grams of fresh dog muscle plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of pure gastric juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the muscle was entirely digested. Cultures of the digest remained sterile. One cubic centimeter represented 125 mg. of muscle.

Solution K (muscle autolysate, infected): Ten grams of fresh dog muscle plus 70 cc. of Ringer's solution was incubated at 37 C. for sixty-eight hours. A scum formed on the surface of the solution, and this was found to contain a luxuriant growth of bacteria (gram-positive cocci and gram-negative bacilli); 0.6 Gm. of solid material remained, so that 1 cc. of the solution represented 118 mg. of muscle.

Solution L (tryptic muscle digest, infected): Ten grams of fresh dog muscle plus 20 cc. of Ringer's solution plus 50 cc. of fresh dog pancreatic juice was incubated at 37 C. for forty-two hours. There was a luxuriant growth of bacteria in the mixture (small gram-negative bacilli and large gram-positive cocci); 0.85 Gm. of solid material remained undigested, so 1 cc. of solution represented 114 mg. of muscle.

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† Probably because of mechanical distention of abdomen.

part by the specific ferments of the gland. The following experiment was performed to test this possibility:

Dog 103.—May 13, 1931: This animal weighed 9.8 Kg. Blood was drawn for chemical examination, with the following result: chlorides, 290; sugar, 86, and nonprotein nitrogen, 32 mg. Under general ether anesthesia and with strict aseptic precautions, the abdomen was opened and a sterile pancreas digest introduced. This digest had been prepared as follows: Sixteen grams of fresh dog pancreas, sterilized in the autoclave at 15 pounds' pressure for fifteen minutes, plus 80 cc. of fresh, active pancreatic juice, sterilized by passage through a Berkefeld U filter, was incubated at 37 C. for sixty-nine hours. The pancreas was about two-thirds in solution, and cultures proved the mixture to be sterile. The entire mixture was placed in the free peritoneal cavity and the abdomen was closed. May 14: The animal recovered from the operation. Its general condition was good. The blood chlorides were 240; sugar, 109, and nonprotein nitrogen, 34 mg. May 26: The animal was in excellent condition. No evidence of toxemia appeared after operation. The animal was electrocuted, and immediate postmortem examination was performed. The peritoneal cavity was entirely normal, with no free fluid, no evidence of peritonitis and no trace of the pancreatic tissue digest.

Comment.—The experimental evidence obtained in this investigation, together with certain observations recorded in the literature, make it appear most probable that the toxemia of acute pancreatic necrosis is due to the absorption of toxic substances produced in the necrotic pancreas by the action of bacteria. Bacteria are present in the uncontaminated pancreas of a high percentage of normal rabbits and dogs, and it is likely that a similar situation obtains in man. In the 10 rabbits examined in this study, bacteria were found in the pancreas in every case, the colon bacillus being the predominant form. A somewhat lower incidence of bacterial contamination was found in the dog. Thirteen of the 17 examined, or 76 per cent, yielded positive cultures, while the cultures for 4 all remained sterile. It should be emphasized that search was made for both anaerobic and aerobic bacteria, and that no cultures were discarded short of two weeks' incubation. In a study made in this laboratory in 1926, Tower found bacteria in the fresh pancreatic tissue of dogs in 15 of the 16 animals operated on. It is probable that these bacteria are present in the duct system of the gland and that they have come from the duodenum, since they are similar in type to the ordinary intestinal organisms. It is clear that under normal conditions they evoke no signs of inflammation in the pancreas. In this respect they are similar to the organisms present in the liver, although it seems probable that in the latter case the bacteria are present in the reticulo-endothelial cells. It is significant that all cultures taken from the necrosing pancreatic tissue of the dogs that died from autolysis of the pancreas yielded an organism very similar to, if not identical with, B. welchii. The predominance of this organism may be due to its having overgrown other forms or to its escape from the gastro-intestinal tract in response to peritoneal irritation very much as occurs in biliary

peritonitis (Andrews, Rewbridge and Hrdina, 1931). The impression that the majority of cases of acute pancreatic necrosis in man are sterile seems to be due to prevailing theories regarding the cause of the disease rather than to the results of bacteriologic study. There have been surprisingly few attempts to culture the necrotic pancreas at operation or immediately after death at autopsy. Larkin (1898) found B. aerogenes-capsulatis, Germain and Christian (1904) streptococci, and Gunther (1909) and Brütt (1923) B. welchii either at postmortem examination or on culture of the peritoneal exudate at operation. The case reported by Gunther is especially interesting in this connection. Cholecystostomy was performed on a patient with acute pancreatitis. Many friable gallstones were found in the gallbladder, and a pure culture of B. welchii was obtained from the gallbladder bile. Death occurred two days after operation, and an autopsy was performed within an hour after death. The pancreas was necrotic, and there was extensive fat necrosis in the peritoneal cavity. A pure culture of B. welchii was again obtained from the necrotic pancreas and from the peritoneal exudate. D. B. Phemister (1930) operated on a patient who had a combination of acute pancreatitis and gangrenous cholecystitis in whom cultures taken from the peritoneal exudate revealed B. welchii in pure culture.

It is true that extracts of many fresh normal tissues yield substances that produce vasodepression and other toxic symptoms if injected into the blood stream of experimental animals. Goodpasture and Clark (1919) were able to secure such substances in extracts of the fresh dog pancreas. Bacteria could have played little or no part in the development of this toxicity, since there was scarcely sufficient time for bacterial activity and growth. It is significant, however, that it required an entire pancreas to yield one fatal dose for an animal of equal weight even when the extract was administered intravenously. As previously noted in cases of acute pancreatic necrosis, the poisons are absorbed from the peritoneal cavity and pass through at least one layer of endothelium before reaching the blood stream. The toxicity of tissue extracts is so greatly reduced by such passage that it is doubtful if the extract secured by Goodpasture and Clark would prove fatal if given in equal amounts intraperitoneally. It must also be kept in mind that the sudden injection of an extract obtained from the pancreas in which the entire dose of toxic material enters the blood stream within a few minutes hardly duplicates the situation which obtains in acute pancreatic necrosis and autolysis. In the latter case, it is reasonable to assume that the responsible poisons are continuously manufactured, liberated and absorbed during the entire period of from eighteen to thirty-six hours. The defensive mechanism of the body is much better able to cope with poisons of the type likely to develop in this instance when

they are slowly administered than when the maximum concentration is presented to the blood stream at once. The amount of toxic material in a watery extract of fresh dog pancreas has no effect if given intra-peritoneally in graduated doses over a period of thirty-six hours to an animal of equal size. We must conclude that during the process of necrosis and autolysis of the pancreas there occurs a marked increase in the amount of soluble toxic material, or that some entirely new poisons are produced.

The experiments offer no support to the view that these toxic substances represent various fractions resulting from the digestion of the dead pancreas by the activated pancreatic juice. The product secured from the digestion of pancreas by pancreatic juice in the absence of bacteria was found to be practically nontoxic on intraperitoneal injection. The innocuous effect of implanting autoclaved pancreas or fetal pancreas, proved to be sterile by culture, into the peritoneal cavity is in harmony with this finding. The implantation of a mixture of ground autoclaved pancreas and active pancreatic juice, proved to be sterile by culture, into the peritoneal cavity without the production of toxemia represents almost a crucial experiment. It proves that neither active pancreatic juice nor the products arising from the digestion of dead pancreas by pancreatic juice within the abdomen are sufficiently toxic when the bacteria commonly found in the intact pancreas have first been removed. The conclusion seems inescapable that in some way these bacteria are necessary for the development of a toxemia in pancreatic necrosis. The exact nature of the poison or poisons remains a speculation. A large variety of toxic chemical fractions might be expected to develop in a mass of necrotic tissue being broken down both by pancreatic juice and by bacterial activity. The frequent finding of B. welchii in the necrotic pancreas suggests that its specific toxin may play a rôle in the disease. It seems more probable, however, that the major amount of responsible poisons will be found among the relatively large group of toxic organic bases that are known to be produced from the decomposition of proteins or protein split products by bacteria or their proteolytic enzymes.

OBSERVATIONS ON THE EFFECT OF ACUTE PANCREATIC NECROSIS ON CERTAIN CONSTITUENTS OF THE BLOOD

An attempt was made in 12 dogs to reproduce the symptoms of pancreatic poisoning by ligating the blood supply to varying amounts of the gland. The postoperative course was carefully observed, and daily determinations were made of the blood chlorides, sugar and nonprotein and urea nitrogen. The blood supply to the tail of the pancreas and to that portion which lies free in the duodenal mesentery was completely occluded in most cases, and careful transfixion sutures in the

duodenal pancreas further decreased its blood supply. Ten of the animals survived the operation and, aside from a moderate postoperative depression, completely recovered. Autopsy at varying periods of from two to five weeks later revealed no evidence of fat necrosis and surprisingly little change in the neighborhood of the pancreas. The free portions of the gland the blood supply of which had been completely interrupted were represented only by thin fibrous cords. The duodenal

TABLE 5.—*Effect of Ligation of the Blood Supply to the Dog's Pancreas on the Blood Chemistry* *

Dog	Days After Pancreas Ligation	Symptoms	Chlorides	Sugar	Nonprotein Nitrogen	Urea Nitrogen
220	0	Normal	301	..	33	15
	1	Lively	300	..	42	17
	2	Slight depression	223	..	82	47
	3	Slight depression	209	..	99	55
	4	Slight depression	204	..	83	53
	5	Lively	206	..	64	..
	7	Condition good	217	..	58	..
152	0	Normal	348	..	48	24
	1	Weak, depressed	289	..	48	23
	2	Weak, depressed	271	..	47	23
	3	Weak, depressed	284	..	43	21
	4	Condition good	278	..	48	23
	5	Condition good	...	..	41	20
999	0	Normal	303	160?	26	12
	3	Slight depression	302	88	23	..
	6	Condition good	316	90	31	14
996	0	Normal	275	79	26	12
	3	Slight depression	321	80	25	13
	7	Condition good	317	74	29	12
940	0	Normal	285	81	29	13
	2	Moderate depression	244	68	33	14
	5	Condition good	267	74	30	12
992	0	Normal	270	77	24	13
	2	Depressed	306	83	21	12
	6	Condition good	301	81	27	12
997	0	Normal	284	81	22	11
	2	Slight depression	251	105	29	..
165	0	Normal	379	..	39	19
	6 hrs.	Condition good	312	..	43	22
	23 hrs.	Severe depression	280	..	93	51
	25 hrs.	Moribund	297	..	118	57
	26 hrs.	Died				
211	0	Normal	303	..	40	14
	5 hrs.	Depressed	292	..	42	20
	24 hrs.	Marked depression	238	..	64	32
	28 hrs.	Marked depression	240	..	87	..
	31 hrs.	Moribund	238	..	86	..
	44 hrs.	Found dead				

* In the experiments necrosis of a part of the pancreas (from one third to one half) was produced by ligating the blood supply.

pancreas was otherwise grossly normal. The data are summarized in table 5.

Similar observations were made of the alterations in the blood chemistry produced by the intraperitoneal autolysis of implanted pancreas in the experiments previously described. The data are summarized in table 6. In both series a decrease in the concentration of blood chlorides and an increase in nonprotein and urea nitrogen were regularly found.

TABLE 6.—*Effect of In Vivo Autolysis of Pancreas on the Blood Chemistry*

Dog	Time After Pancreas Implantation	Symptoms	Chlorides	Sugar	Non-protein Nitrogen	Urea Nitrogen	Comment
956	0	Normal	330	84	33	14	Roughly ½ of a pancreas obtained from another dog was wrapped in omentum and abdomen closed
	24 hrs.	Vomiting, toxic	166	38	45		
	32 hrs.	Died					
945	0	Normal	255	..	24	10	Roughly ¾ of a pancreas obtained from another dog was placed in the free peritoneal cavity and abdomen closed
	23 hrs.	Very toxic	250	..	54	33	
	47 hrs.	Very toxic	161	..	53	36	
	70 hrs.	Found dead					
949	0	Normal	278	..	27	13	About ½ of a pancreas obtained from another dog was placed in the free peritoneal cavity and abdomen closed
	23 hrs.	Very toxic	221	..	26	12	
	48 hrs.	Improved	254	..	30	14	
	72 hrs.	Purulent nasal discharge, cough	218	..	27	8	
	73 hrs.	Animal killed with ether; lobar pneumonia					
800	0	Normal	306	..	26	13	Roughly ½ of a pancreas obtained from another dog was placed in the free peritoneal cavity and the abdomen closed
	1 day	Slight depression	295	..	53	27	
	2 days	Slight depression	248	..	38	8	
	4 days	Condition good	240	..	23	13	
	6 days	Condition good	312	..	21	11	
	7 days	Condition good	326	..	19	11	
	9 days	Condition good	302	..	15	7	
	12 days	Condition good	329	..	19	12	
	19 days	Condition good	329	..	19	12	
	42 days	Condition good	313	..	17	10	
	42 days	Killed with ether					
916	0	Normal	287	..	25	11	About ½ of a pancreas obtained from another dog was placed in the free peritoneal cavity and the abdomen closed
	1 day	Slight depression	265	..	24	12	
	2 days	Slight depression	223	..	53	32	
	4 days	Condition good	222	..	45	26	
	6 days	Condition good	210	..	48	29	
	7 days	Condition good	268	..	36	16	
	9 days	Condition good	275	..	21	12	
	12 days	Condition good	316	..	20	10	
	19 days	Condition good	296	..	23	12	
	41 days	Killed with ether					
513	0	Normal	339	84	25	13	The entire pancreas obtained from a dog weighing 13.4 Kg. was placed in the free peritoneal cavity and the abdomen closed
	22 hrs.	Died					
732	0	Normal	298	90	29	12	The entire pancreas obtained from a dog weighing 21 Kg. was placed in the free peritoneal cavity and the abdomen closed
	18 hrs.	Died					
629	0	Normal	310	89	26	12	The entire pancreas obtained from a dog weighing 13.4 Kg. was placed in the free peritoneal cavity and the abdomen closed
	21 hrs.	Moribund	220	72	56	28	
	25 hrs.	Died					
419	0	Normal	200	..	24	11	The entire pancreas from another dog was placed in the free peritoneal cavity and the abdomen closed
	26 hrs.	Died					
588	0	Normal	295	..	22	13	An entire pancreas weighing 30 Gm. was placed in the free peritoneal cavity and the abdomen closed
	5 hrs.	Slight depression	271	..	24	7.5	
	22 hrs.	Moderate depression	234	..	52	24	
	29 hrs.	Moribund	317	..	75	50	
	34 hrs.	Died					
636	0	Normal	304	..	25	10	An entire pancreas weighing 35 Gm. was placed in the free peritoneal cavity and the abdomen closed
	6 hrs.	Moderate depression	303	..	24	18	
	22 hrs.	Found dead					
788	0	Normal	343	..	24	7	An entire pancreas weighing 30 Gm. was placed in the free peritoneal cavity and the abdomen closed
	6 hrs.	Slight depression	261	..	25	12	
	23 hrs.	Found dead					

TABLE 6.—*Effect of In Vivo Autolysis of Pancreas on the Blood Chemistry—Continued*

Dog	Time After Pancreas Implantation	Symptoms	Chlorides	Sugar	Nonprotein Nitrogen	Urea Nitrogen	Comment
548	0	Normal	273	..	26	12	An entire pancreas weighing 35 Gm. was placed in the free peritoneal cavity and the abdomen closed
	24 hrs.	Depression, marked weakness	275	..	45	25	
	29 hrs.	Condition better	224	..	48	24	
	2 days	Condition good	208	..	24	12	
	3 days	Condition good	278	..	23	11	
	4 days	Condition good	283	..	28	12	
	7 days	Condition good	274	..	27	12	
	19 days	Condition good	314	..	30	8	
787	0	Normal control	320	..	36	8	An entire pancreas weighting 35 Gm. was placed in the peritoneal cavity and the abdomen closed
	7 hrs.	Marked depression and weakness	266	..	27	11	
	24 hrs.	Very toxic	339	..	32	12	
	29 hrs.	Condition better	249	..	40	17	
	48 hrs.	Further improvement	256	..	24	0	
	54 hrs.	Condition good	256	..	19	8	
	72 hrs.	Condition good	276	..	18	6	
	79 hrs.	Condition good	266	..	16		
	96 hrs.	Condition good	253	..	17		
	103 hrs.	Condition good	263	..	15	9	
	5 days	Condition good	338	..	15		
396	0	Normal control	266	..	27	11	An entire pancreas weighing 35 Gm. was placed in the peritoneal cavity and the abdomen closed
	23 hrs.	Marked depression and weakness	251	..	28	..	
	29 hrs.	Condition better	226	..	29	12	
	48 hrs.	Further improvement	226	..	26	13	
	4 days	Moderate depression and weakness	168	..	39	20	
	9 days	Condition good	259	..	19	7	
	12 days	Condition good	272	..	20	8	
	19 days	Condition excellent	326	..	23	8	
	40 days	Condition excellent	302	..	24	12	

During the course of these studies an opportunity presented itself to examine the blood chemistry in a patient with a mild but undoubted case of acute pancreatitis. The pertinent features of the history are given here.

J. H., a man, aged 49, came to the hospital with symptoms and findings suggestive of chronic cholecystitis. Thirty-six hours later he experienced a sudden severe pain in the left upper quadrant of the abdomen, accompanied by a drenching perspiration and symptoms of vascular collapse. The blood pressure fell to 88 mm. systolic. A diagnosis of acute pancreatitis was made, and operation was performed immediately. The pancreas was indurated, and there were numerous areas of fat necrosis. No stones were found in the gallbladder or common bile duct. The wall of the gallbladder was thickened. A drain was placed in the gallbladder and in the lesser peritoneal cavity. Each twenty-four hours for the next five days 3,000 cc. of Ringer's solution was given subcutaneously or intravenously. The results of the chemical examination of the blood are summarized in table 7.

Here again, as in the animal experiments, a decrease in the concentration of blood chlorides and an increase in nonprotein and urea nitrogen are the most prominent changes. These alterations are similar to those which occur in acute intestinal obstruction or following the failure of reabsorption of gastric and pancreatic juice. It is probable that they can be accounted for in a similar way. The extensive perito-

neal irritation resulting from the in vivo autolysis of the pancreas might
be expected to produce a profound reflex inhibition of gastro-intestinal
motility. A paralytic ileus, more or less severe, is commonly found in
acute pancreatitis in man. The relation of such disturbances in motility
to the blood chemistry has been discussed by one of us in considerable
detail elsewhere (L. R. D., 1930). Under normal conditions, the
gastric and pancreatic secretions poured into the upper part of the
alimentary tract are more or less completely absorbed in the intestine
lower down. Water and inorganic salts, the principal constituents of
these secretions, are not appreciably absorbed in the stomach, duodenum
or even upper part of the jejunum. It is clear, then, that for reabsorp-
tion, the gastric and pancreatic juice must be carried by the motor
activities of the intestine into the ileum and colon. Interference with
this transport, such as occurs in paralytic ileus, must result in the loss
of the various constituents of these secretions to the body either

TABLE 7.—*Blood Chemistry in a Case of Acute Pancreatitis*

Time After Operation, Days	Condition	Blood Chemistry				
		NaCl, Mg.	CO_2 Capacity, Cc.	Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Sugar, Mg.
1	Sick, vomiting	335	55	58	36	...
2	Very sick, vomiting	458	50	102	76	125
3	Improved, no vomiting	464	57	86	66	...
4	Improved, no vomiting	492	63	76	52	152
5	Marked improvement	490	73	50	31	118

through vomiting or through accumulation of the lumen of the non-
absorbing portions of the tract. The failure of reabsorption of the
sodium and chloride ions present in gastric and pancreatic juice leads
to the development of hypochloremia, alkalosis and dehydration, because
the stomach (L. R. D. and I. C. E., 1930) and pancreas (Elman and
McCaughan, 1927, and Gamble and McIver, 1928) have the property of
separating these ions from the blood stream irrespective of their concen-
tration there, even though such separation so greatly alters the chemical
composition of the blood that life can no longer exist.

TREATMENT

While this investigation has been concerned primarily with the
pathogenesis of acute pancreatitis, it may be worth while to note briefly
certain inferences toward treatment that have suggested themselves.
The poison or poisons responsible for this dread toxemia have not yet
been defined in precise chemical terms, and until this is done there will
be little hope of developing a specific antitoxic therapy. It is exceed-
ingly important that this be done, since undoubtedly many patients have
absorbed a fatal dose of this toxic material into the blood stream, and

it has become fixed in the tissue cells, before they come to treatment. The trial of B. welchii antitoxin would appear to be justified by the almost regular finding of this organism in the necrotic pancreas in these animal experiments. Needless to say, great caution should be observed in interpreting the results secured. It is our opinion, however, that not until we have secured an adequate therapy for the toxemias produced by the nonantigenic proteinogenous amines and other products of bacterial proteolysis will this part of the problem be solved.

At present, we are largely limited to attempts to prevent further injury to the pancreas and the entrance of additional poison into the blood stream. The suggestions of Archibald (1929) here seem most reasonable in the light of this study. Since in all probability the majority of cases are due to the passage of bile into the pancreatic ducts, it seems wise to reduce the pressure in the biliary tract and divert the bile and possibly the pancreatic juice as well to the exterior by means of cholecystostomy or choledochostomy. The drainage tube might well be connected to a negative pressure bottle. In view of the greatly increased susceptibility of etherized animals to histamine, it is probably safer to use local than general anesthesia. While the studies of Whipple and Goodpasture (1913) and Peterson, Jobling and Eggstein (1916) indicate that the abdominal exudate is nontoxic, we believe it is advisable to place drains about the pancreas. This is done not so much with the thought of draining away toxic material as to facilitate the formation of adhesions and the isolation of the necrotic pancreas from the remainder of the abdomen. The intravenous administration of physiologic solution of sodium chloride or Ringer's solution is advisable to correct the alterations in the blood chemistry and the dehydration accompanying the paralytic ileus. It is possible that the parenteral administration of large amounts of salt solution with the ensuing diuresis may facilitate the excretion of soluble toxic chemicals from the blood stream and so exert a dual beneficial effect. Repeated gastric aspirations prevent overdistention and enable the stomach to recover its tonus more quickly.

CONCLUSIONS

It is probable that about 60 per cent of the cases of acute pancreatic necrosis in man arise in patients with antecedent chronic biliary tract disease. Of these, it is likely that 10 per cent develop a common channel as a result of the impaction of a gallstone in the ampulla and a majority of the remainder a similar continuous channel through spasm of the sphincter of Oddi or edema of the papilla. In this group, the immediate cause of the necrosis is the passage of bile over into the pancreatic ducts which is made possible not so much by a difference in secretory pressures of the liver and pancreas as by the fact that the

intraglandular anastomoses between the ducts of Wirsung and Santorini make the secretory pressure of the pancreas ineffectual in the majority of cases. Bile produces necrosis of the pancreatic parenchyma because of the local cytolytic and destructive properties of the bile salts and not through activation of the intraductal trypsinogen of the pancreatic juice. The toxic effect of the bile salts is neutralized by the proteins of the blood serum, so that hemorrhage and exudation are protective phenomena. The digestion of the protective proteins of the serum by the proteolytic enzymes of the pancreatic juice frees the bile salts for further destructive action, and this probably accounts for the greater susceptibility of the pancreas to biliary necrosis than is found for other glandular organs. A typical pancreatic necrosis may, however, be produced by a variety of factors, listed in the foregoing discussion, in which bile plays no part. The discovery of instances in which a common continuous channel of the bile and pancreatic ducts is an anatomic impossibility can, accordingly, not be construed as evidence against the bile factor in pancreatitis, since it merely shows that it is not operative in the particular cases studied. There is no good evidence that the intraductal or intraglandular activation of trypsinogen will cause self-digestion of the pancreas. Active trypsin was found to be incapable of digesting living tissues. It is probable that trypsin has no corrosive properties in itself which would injure living cells and that it acts only as a catalyst in facilitating the hydrolysis of proteins by the alkali of the pancreatic juice. The locally destructive action of pancreatic juice is dependent on its concentration of alkali just as the corrosive effect of gastric juice is dependent on its concentration of free acid.

It is probable that irrespective of whether the necrosis of the pancreas is due to the invasion of bile, to trauma, to vascular injury or to infection, the cause of the resulting toxemia is the same. The amount of pancreatic juice or of its constituent enzymes which could be present in the necrotic pancreas is insufficient to account for the toxic effect. Inactive pancreatic juice was found to be nontoxic if allowed to flow into the free peritoneal cavity. The active lipase of this secretion was unable to digest the lipoid envelop of living cells and produce necrosis. The areas of so-called fat necrosis found probably represent already dead cells the fat of which has been converted into glycerin and fatty acids by the pancreatic steapsin, after which the fatty acids have combined with calcium to form soaps. It is probable that in acute pancreatitis the fat necrosis is due more to the destructive action of bile than to that of pancreatic juice. The digestion of the fat is brought about by the latter secretion. The intraperitoneal injection of actively proteolytic pancreatic juice was found to be no more toxic than the intraductal secretion if bacterial contamination was avoided. As much

as 110 cc. of a Berkefeld filtrate of active pancreatic juice was injected into the free peritoneal cavity without causing toxemia. The end-products of the partial or complete digestion of the pancreas by active pancreatic juice are not sufficiently toxic, if placed in the peritoneal cavity, to cause death. The in vivo autolysis of sterile fetal pancreas and the intraperitoneal digestion of autoclaved pancreas by sterile pancreatic juice did not produce toxemia. The uncontaminated pancreases of 10 living, adult, normal, rabbits yielded positive bacterial cultures in every instance, or 100 per cent. In 13 of 17 dogs similarly examined, bacteria of various types were found in the uncontaminated pancreas. These bacteria were similar to those common to the intestinal tract. B. welchii was especially prevalent. The toxemia resulting from experimental in vivo autolysis of the pancreas is chiefly due to the presence of these organisms, which proliferate in the necrotic tissue. It is possible that the toxin of B. welchii may contribute to the toxic effect, but it seems probable that the major part of the toxemia is due to the group of proteinogenous amines and similar substances arising from the bacterial decomposition of proteins or their split products.

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EXPERIMENTAL OBSTRUCTION OF JEJUNUM

EFFECT OF ADMINISTRATION OF WATER ON LENGTH OF LIFE AND CHANGES IN CHEMICAL COMPOSITION OF BLOOD

HJALMAR E. CARLSON, M.D.

AND

THOMAS G. ORR, M.D.

KANSAS CITY, KAN.

It is well recognized that there is a decrease in chlorides and an increase in the carbon dioxide-combining power and in the nonprotein nitrogen and the urea nitrogen of the blood in intestinal obstruction. The rôle played by water, when administered by mouth, on the extent of these changes and on length of life has been little studied. A more thorough investigation was thought indicated, particularly since determinations of the chemical composition of the blood are being increasingly used as a guide for treatment of obstruction of the pylorus and small bowel.

In an earlier study of the changes occurring in the blood incident to high intestinal obstruction, the average length of life of dogs was observed.[1] These animals were allowed as much water as they wanted, and the average length of life of thirty-five dogs in which the upper part of the jejunum was obstructed was 6.8 days. Hartwell and Houguet [2] obstructed the jejunum of dogs from 10 to 30 cm. below the pylorus and found that few lived longer than five days. They also found that dogs deprived of food from forty-eight to seventy-two hours before obstruction would die as early as those fed from ten to twenty hours before obstruction. Wangensteen [3] says that the average length of life of dogs with high intestinal obstruction is from three to four days. Dragstedt and Moorhead [4] obstructed the duodenum of dogs below the pancreatic duct, and all the animals died in less than ninety-six hours.

1. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. 37:365, 1923.

2. Hartwell, J. A., and Houguet, J. P.: An Experimental Study of Intestinal Obstruction, Am. J. M. Sc. 143:357, 1912.

3. Wangensteen, O. H.: The Diagnosis and Treatment of Acute Intestinal Obstruction, Northwest Med. 30:389, 1931.

4. Dragstedt, L. R., and Moorhead, J. J.: Immunity in Intestinal Obstruction, J. Exper. Med. 27:359, 1931.

MATERIALS AND METHODS

In this study intestinal obstruction was produced in twelve healthy dogs by sectioning and inverting the cut ends of the jejunum 15 cm. below the ligament of Treitz. All operations were done under ether anesthesia with aseptic technic. Six dogs were allowed water ad libitum after the operation, and six were entirely deprived of water. None of the dogs received food after the operation, nor was any food given twenty-four hours prior to the operation. The animals were kept in clean metabolism cages, and the body weight taken daily. An autopsy was always performed. Peritonitis was never a complicating factor.

TABLE 1.—*Obstruction of the Upper Jejunum of the Dog When No Water Was Allowed*

Dog	Day After Obstruction	Blood, Mg. per 100 Cc.			Carbon Dioxide-Combining Power, per Cent by Volume	Body Weight, Kg.	Comment
		Chlorides, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.			
1	0	510	12.3	73.2	43.9	13.85	Fat dog; length of life,
	1	442	19.6	75.4	49.5	12.75	36 hours
2	0	515	17.1	71.4	45.8	7.36	Moderately fat dog;
	1	490	14.4	93.0	55.1	6.75	length of life, 56 hours
	2	510	55.6	119.0	46.5	6.30	
3	0	515	11.4	75.7	51.4	11.30	Fat dog; length of life,
	1	400	8.1	83.3	52.3	10.55	60 hours
	2	460	18.5	100.0	51.2	10.40	
4	0	510	7.7	67.7	46.2	8.80	Moderately fat dog;
	1	467	7.4	109.8	50.9	8.45	length of life, 80 hours
	2	400	13.3	81.6	53.7	8.02	
	3	450	15.7	119.0	57.5	7.75	
5	0	542	11.9	56.5	47.7	7.25	Fat dog; length of life,
	1	467	9.0	76.9	52.5	6.85	130 hours
	2	480	13.9	52.2	52.8	6.65	
	3	505	15.7	62.5	57.5	6.41	
	4	480	16.3	64.9	54.7	6.13	
	5	470	46.7	88.2	52.0	..97	
6	0	520	9.9	60.7	49.0	13.25	Fat dog; length of life,
	1	463	7.5	111.0	52.8	12.80	130 hours
	2	380	12.5	60.6	54.7	12.20	
	3	420	14.5	100.0	55.6	11.63	
	4	425	59.1	94.3	55.1	11.24	
	5	385	84.0	80.4	50.2	11.05	

Blood for chemical analysis was obtained from the jugular vein before operation and at twenty-four hour intervals thereafter until the death of the animal (tables 1 and 2). The blood chlorides were determined on the tungstic acid filtrate, as suggested by Gettler.[5] The blood for the carbon dioxide-combining power was collected under oil and determined by the method of Van Slyke and Cullen;[6] the urea nitrogen was determined by the Van Slyke and Cullen[7] modi-

5. Gettler, A. O.: Method for Determination of Death by Drowning, J. A. M. A. **77**:1650 (Nov. 19) 1921.

6. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: The Bicarbonate Concentration of the Blood Plasma; Its Significance and Its Determination as a Measure of Acidosis, J. Biol. Chem. **30**:289, 1917.

7. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use for Rapid and Accurate Determination of Urea, J. A. M. A. **62**:1558 (May 16) 1914.

fication of the Marshall method, and the sugar by the method of Folin and Wu.[8] The protein-free blood filtrates were made by Haden's modification of the original Folin-Wu technic.[9]

TABLE 2.—*Obstruction of the Upper Jejunum of the Dog When the Animals Were Permitted to Drink Water ad Libitum*

| Dog | Day After Obstruc- tion | Blood, Mg. per 100 Cc. | | | Carbon Dioxide- Combining Power, per Cent by Volume | Body Weight, Kg. | Comment |
		Chlorides, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.			
1	0	480	12.6	59.4	48.5	7.45	Moderately fat dog; length of life, 66 hours
	1	444	32.8	81.3	49.2	7.05	
	2	383	36.4	72.2	53.7	6.75	
2	0	525	18.2	68.1	42.5	7.65	Moderately fat dog; length of life, 116 hours
	1	407	18.5	80.9	47.7	7.20	
	2	385	27.6	87.3	63.2	6.90	
	3	365	·50.8	78.7	67.2	6.85	.
	4	293	85.3	117.6	67.1	6.60	
	5	260	122.0	207.0	41.6	6.15	
3	0	530	7.7	85.1	53.7	9.60	Moderately fat dog; length of life, 158 hours
	1	475	6.9	84.4	52.3	8.76	
	2	455	4.7	77.1	53.1	8.83	
	3	460	7.2	62.1	52.4	8.55	
	4	392	13.5	84.0	51.8	8.25	
	5	351	32.1	105.1	58.1	7.95	
	6	293	55.2	114.1	65.5	7.60	
4	0	485	12.2	59.7	43.7	9.95	Moderately fat dog; length of life, 260 hours
	1	470	13.7	77.8	48.4	9.85	
	2	395	12.2	72.7	48.1	9.65	
	3	422	9.1	94.4	46.3	9.75	
	4	456	5.5	80.3	58.4	9.40	
	5	435	9.8	79.9	52.8	9.38	
	6	456	9.8	70.4	50.6	9.05	
	7	430	10.1	66.8	54.0	8.95	
	8	400	10.3	62.7	54.2	8.65	
	9	425	33.1	128.1	65.4	8.53	
	10	429	41.1	351.0	35.2	7.93	
5	0	460	7.8	62.5	51.3	12.55	Fat dog; length of life, 264 hours
	1	418	9.8	77.6	57.5	12.50	
	2	379	8.4	67.2	59.3	12.25	
	3	400	10.6	67.8	62.1	12.15	
	4	429	13.3	76.1	66.6	11.80	
	5	380	13.8	76.6	70.6	11.35	
	6	349	11.7	75.7	70.3	11.15	
	7	350	18.7	71.3	71.4	10.85	
	8	330	14.1	79.4	72.8	10.65	
	9	248	44.4	100.2	78.1	10.20	
	10	271	56.8	104.8	79.1	9.93	
	11	202	72.8	164.0	101.2	9.35	
6	0	490	6.1	70.1	57.2	16.80	Fat dog; length of life, 182 hours
	1	408	8.9	74.2	59.0	16.40	
	2	425	15.3	67.9	56.7	15.95	
	3	440	15.9	57.6	60.6	15.75	
	4	412	32.7	65.8	58.7	15.65	
	5	391	58.1	65.2	58.1	15.35	
	6	344	59.0	86.6	54.4	15.35	
	7	280	62.8	93.0	59.3	14.00	
	8	295	93.8	113.8	64.5	13.88	

8. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

9. Haden, R. L.: A Modification of the Folin-Wu Method for Making Protein-Free Blood Filtrates, J. Biol. Chem. **56**:469, 1923.

OBSERVATIONS AND COMMENT

As the experiment progressed, the blood chlorides of the dogs receiving no water showed only a small drop compared with those of the dogs that were allowed water. The greater fall in chlorides found in the animals receiving water is probably due to a washing of the chlorides from the stomach and upper intestine by persistent vomiting. Dogs receiving water showed a greater rise in carbon dioxide-combining power. The urea nitrogen showed the characteristic increase in both series. The increase was generally most marked in the animals living the longest. There was an increase in blood sugar in every animal in each series. The greatest change was found in the animals living longest.

In spite of the lesser effect on the chemical composition of the blood shown in the animals to which no water was given, these animals did not live so long as those that were allowed water and that showed marked changes in the blood. The average length of life of the animals not receiving water was eighty-two hours, while those receiving water lived an average of one hundred and seventy-two hours.

A study of the body weights shows that the rate of loss in weight was not so rapid in the animals receiving water as in those that did not. This would point to some absorption of water from the upper gastro-intestinal tract, which may in part explain the greater length of life of these animals. The state of nutrition of the animals did not appear to have any bearing on the length of life.

SUMMARY

1. The upper part of the jejunum was obstructed in twelve healthy adult dogs. Six of them were deprived of both food and water, and six were deprived of food but given water freely.

2. The animals deprived of water showed relatively little change in the blood chlorides, carbon dioxide-combining power and sugar compared to the animals to which water was freely administered.

3. The animals showing great change in the chemical composition of the blood lived longer than the animals showing little change.

4. The rate of loss in body weight was slower in the animals receiving water than in the animals deprived of water. This would suggest that water absorbed from the upper gastro-intestinal tract helped to prolong the lives of the animals.

5. These experimental findings suggest that continuous lavage of the stomach in acute intestinal obstruction is a beneficial part of the treatment.

THE PART PLAYED BY URETERAL INFLAMMA-TION IN DILATATION OF THE URETER

A POSTMORTEM STUDY

DOUGLAS E. SCOTT, M.B.

GREENWICH, CONN.

That dilatation of the ureter will result from obstruction is apparent, but that it may be acquired in the absence of any form of mechanical obstruction is perhaps less obvious and at first glance paradoxical. Atony of the ureter, by which is meant loss of functional ability of the muscle of the ureter, whereby peristalsis is weak or absent, was first recognized by Russian observers as a cause of ureteral dilatation. Further, they conceived the idea that atony and dilatation may result from inflammation. In this country Braasch repeatedly has called attention to this inflammatory dilatation, but by most observers such a possibility has not been appreciated or has been frankly doubted.

It is also true that certain obstructive factors commonly assumed to cause ureteral dilatation are in fact of obscure mechanism. Thus, there has been much speculation over the ureteral dilatation which accompanies pregnancy, and also over that which occurs with prostatic obstruction. The frequent association of these questionable obstructive factors with ureteral infection makes any appraisal of the part the latter may play a matter of interest. It was for the purpose of investigating these aspects of ureteral dilatation that I undertook this study. The extensive review of the literature which preceded my own work is omitted from this paper.

MATERIAL

The material investigated was obtained at necropsy in one hundred unselected cases. The causes of death were representative of many types of disease. Sixty-eight subjects were males and thirty-two were females. All decades of life up to the ninth were represented; there were eight subjects in the first decade.

METHOD

In each case the ureters were carefully inspected in situ. Their relation to surrounding structures and the relation of the state in which they appeared to any disease of surrounding structures were noted. This included attention to the

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presence of supernumerary vessels to the kidney, to the effect of pressure from the ductus deferens, and to the seminal vesicles, bladder, prostate gland, urethra and female pelvic structures. A no. 24 French urethral sound was passed in each case in which, judging from the history or from the lesions found, urethral stricture might have been a factor.

The ureters were then carefully removed, with the kidneys, bladder and prostate gland attached, and the bladder was opened anteriorly for inspection. In eighty-eight cases, ureterograms or pyelo-ureterograms were then made in the following manner:

The pelves and ureters were first gently stripped to insure complete emptying. Tips of Garceau catheters were tied lightly within the ureteral orifices by a stitch taken in the surrounding vesical tissue, and the ureters and pelves were filled by gravity from a height of 34 cm. A 30 per cent solution of sodium bromide was used. This solution at this height has a pressure equivalent to 30 mm. of mercury. This pressure filled the ureter gently. In two cases incomplete filling was noted. However, the least possible pressure seemed desirable, and this pressure probably approximated that used clinically.

The contour of the ureter was observed as it filled, and the amount of solution required to fill the pelvis and ureter was recorded. The place where the internal diameter of the ureter was smallest was found, and was measured by passing ureteral bulbs. The bulbs were tried in decreasing sizes on the French scale, until one was found which would enter and pass up the ureter without meeting obstruction to very gentle pressure. The largest bulb which would just pass in this way was taken as the smallest diameter of the ureter.

The widest diameter of each ureter was measured after the ureter had been opened longitudinally along its anterior aspect. By gently extending the ureter to the limits of its lateral elasticity, the internal circumference could be measured and the diameter calculated. In a third of the cases the diameter at the narrowest point was measured in this way. The diameter of the ureter when measured on the roentgenogram was found to correspond closely with the internal diameter measured on the ureter at the same level. Discrepancies which occurred in some cases were due to the filled ureter being markedly oval rather than cylindric.

From two to six cross-sections, including the whole circumference, were taken from various levels of each ureter for microscopic study. These were stained with hematoxylin and eosin, and by van Gieson's method for fibrous tissue.

The measurements and roentgenograms were completed in from two to four hours after death in most cases, so that postmortem changes affecting the distensibility of the ureter were negligible, except as will be referred to later. The average examination was complete within six hours after death, and not more than twelve hours elapsed between death and completion of the examination in any case. With each case the history was reviewed for symptoms or clinical findings possibly referable to the urinary tract, and especially for lesions of the central nervous system which might affect the nervous mechanism of the urinary tract.

The data from which information was drawn may be summarized as follows: (1) clinical history and examination, (2) inspection of the ureter in situ, (3) contour of the filled ureter after removal, (4) the measured internal diameter, (5) measurements of the capacity of the ureter and pelvis, (6) ureteropyelograms (post mortem) and (7) microscopic sections.

In deciding the status of any ureter, it must be remembered that individual variations in form and size are great, and that any set standards for the normal, although helpful, must be arbitrary and may mislead. Since it was realized that normally narrow ureters may become dilated and still be in the range of many

of the quoted normal figures, and that ureters in the same person, although usually resembling each other in general contour and type, need not do so, each ureter was considered on its own merits, in the light of data accumulated from all available sources.

DIAMETER

Measurements of internal diameter were made of seventy-two normal right ureters and of seventy-three normal left ureters of adult subjects. Measured at the widest point of each ureter, the average diameter of the right ureter was 6.2 mm., and that of the left ureter, 5.6 mm. The variation was from 3 to 9.5 mm. Measured at the narrowest point of each ureter, the average diameter was 2.6 mm. for both right and left ureters, the variation. being from 1.3 to 4.6 mm. The situation of the narrowest point of the ureter was at the orifice in 31 per cent of cases and in the lowest 4 cm. in 82 per cent of cases.

CAPACITY

Measurements of the capacity of the ureter and pelvis of adults were made in forty-nine cases on the right side and in fifty-three cases on the left side. The average capacity on the right side was 11.5 cc., and that on the left, 10.5 cc. The variation on the right side was from 5 to 20 cc., and that on the left side was from 4.5 to 18 cc., except in one case. In this case, in which the ureters and pelves must be considered to have been normal, the capacity was 30 cc. The subject was very large, and died of myocardial failure. The right kidney weighed 187 Gm., and the left, 227 Gm. The kidneys appeared normal, except that a large, solitary cyst was observed on the convex border of the left kidney. There was no reason to believe that this had in any way interfered with renal drainage. There was considerable hypertrophy of the prostate gland, but without evidence of obstruction to the bladder. The ureters were normal. The large capacity was evidently due to the unusual number of large, branching calices. The capacity of the corresponding kidney could not be accurately measured because of the readiness with which pyelovenous backflow occurred.

OCCURRENCE OF URETERAL STRICTURE

Clinical determination of ureteral stricture has been by the "hang" of the ureteral bulb and by the ureterographic shadow. The fallacy of the bulb method was demonstrated by Frater in postmortem study of ninety-three cases, and his experience was confirmed in the present series. Repeatedly, in cases in which hang was obtained, there was no microscopic or gross evidence of stricture.

The pyelographic evidence of ureteral stricture is localized narrowing of the ureteral shadow, with dilatation of the ureter above. *Ureteral*

spasm is distinguished from stricture by absence of dilatation above the narrowing. Incomplete filling must also be distinguished.

In considering the question of ureteral stricture, it has been assumed heretofore, in postmortem studies, that the factor of spasm is eliminated. That spasms do occur post mortem was repeatedly demonstrated in this series of ureters.

Narrowings of the ureterographic shadow occurred not infrequently in this series. They suggested spasm in that there never was dilatation above them. Also, they occurred more often in ureterograms taken soon after death than in those taken after some delay. In one case the narrowing was sufficient completely to block injection of the medium until a pressure of 100 mm. of mercury was reached, when a normal renal pelvis was outlined above.

In another case it was possible gently to expose the right ureter half an hour after death. Pinching with forceps sent the upper third of the ureter into visible spasm, which persisted until the pyelogram was taken an hour later. On opening the ureter at the point of narrowing, the mucosa was seen to be in the longitudinal folds characteristic of contraction. Microscopic sections taken at these narrow points showed no evidence of stricture; that is, the ureteral structure was normal, without increase in fibrous tissue or evidence of inflammatory process. Evidently, then, these narrowings are caused by spasm.

Stricture of the ureter of intrinsic inflammatory origin has been the subject of many clinical reports and much controversy in the past. As has just been shown, the clinical difficulties of demonstration of stricture also exist for the gross determination of stricture after death. In the latter case, however, microscopic check on the diagnosis is possible. With inflammatory stricture there should be microscopic evidence of its presence. Such stricture, due to localized increase of connective tissue, the result of a primary inflammatory process in the ureteral wall, was not found in this series of cases.

Narrowings of the ureteral lumen which were evidently interfering with ureteral function, since there was dilatation above them, occurred in four cases. Two of these were strictures at the orifice, the result of vesical disease. In one of these two cases, the narrowing was the result of infiltration by a tumor, and in the other, of inflammatory reaction to surgical diathermy. In the other two cases the narrowing was caused by involvement of the ureter in periureteral scar tissue which had formed postoperatively.

URETERAL DILATATION

In twenty-five of the hundred cases, dilatation of one or both of the ureters or pelves was found. In a number of cases, at necropsy, the cause of the dilatation was found to be obstruction. In other cases,

obstruction had been present previously, as was noted from the histories of the cases. In another group of cases, however, there was neither obstruction nor a history of obstruction. Consideration of a number of cases of this group made it seem evident that infection of the ureteral wall, leading to atony, was the cause of the dilatation. In other cases, in which obstruction was present, inflammation undoubtedly was a contributory factor.

The causes of ureteral dilatation in this series may be grouped as follows: stricture of the ureter resulting from local causes, four cases; mechanical obstruction from an aberrant renal vessel, from a fibromyoma of the uterine cervix or from a vesical tumor, one case each; stone with ureteritis, two cases; pelvic inflammation involving a length of the ureter, two; pregnancy, one case; multiparity associated with ureteritis, four cases; prostatic hypertrophy associated with infection, three; insufficiency of ureteral valve, due to inflammation, two; inflammation of the ureter with no other associated cause, four; neurogenic origin (questionable), one case, and congenital origin, one.

The following cases are selected as illustrative of the part played by inflammation in causing dilatation of the ureter.

REPORT OF CASES

CASE 1.—*Prostatism and ureteral infection.*

A man, aged 74, with a history of obstructive vesical symptoms for eight years, died of renal insufficiency ten days after cystostomy.

At necropsy, little, if any, enlargement of the prostate gland was found. It was, however, inflamed and contained many calculi. There were marked hypertrophy of the vesical wall, with many cellules, and severe cystitis. Both ureters and renal pelves were found enormously dilated. On the right side the capacity was 75 cc., and on the left side, 95 cc. The right ureter varied in diameter from 3.3 mm. at the orifice to 16.6 mm. at its widest part. The diameter of the left ureter varied from 3.6 mm. at the orifice to 13 mm. at its widest part. The mucosa of each appeared injected and edematous throughout.

Microscopically, both ureters presented the appearance of acute infection superimposed on chronic infection. The submucosal layer was edematous and infiltrated with polymorphonuclear leukocytes. There was much young connective tissue with large and small lymphocytes. The muscular layer was poorly stained and infiltrated with polymorphonuclear leukocytes. The adventitia was characterized by groups of lymphocytes and young connective tissue cells. The prostate gland was evidently obstructing the bladder. However, it was notable that although the wall of the bladder was greatly thickened the diameter of the intramural portion of the ureter was more than the average. Such a condition is difficult to reconcile with the view that the hypertrophied vesical wall obstructs the ureters. The idea that the lower part of the ureter becomes distorted by enlargement of the prostate gland is not applicable here, since actual enlargement of this gland was negligible. Whatever the cause of obstruction to the ureters in cases of prostatic disease, infection may be considered a frequent contributory factor to the dilatation.

CASE 2.—*Incompetence of the ureteral orifice caused by inflammation.*

A man, aged 67, died of acute diffuse pyelonephritis and bronchopneumonia. Nine years previously a papilloma had been removed from the bladder. Since then he had had increasing frequency and occasional hematuria on straining.

Necropsy disclosed suppuration but only slight enlargement of the prostate gland. The bladder was of small capacity, of irregular shape, much scarred and acutely inflamed. The right ureteral orifice was gaping and rigid. Regurgitation through it had been demonstrated a week before death. A pyelogram made post mortem gave evidence of a normal left ureter and pelvis. The right ureter and pelvis were markedly dilated, with a capacity of 35 cc. (fig. 1). The internal diameter of the right ureter varied from 3.3 to 11 mm. The kidney was atrophied, and weighed only 50 Gm. Sections of the intramural portion of the right ureter,
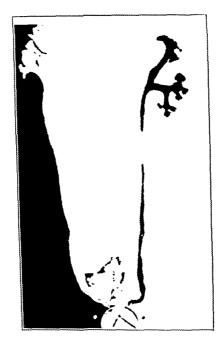
Fig. 1 (case 2).—Right ureteral dilatation due to gaping ureteral orifice, the result of infection.

as well as of the same ureter higher up, contained masses of lymphocytes and young connective tissue cells in all the layers. It was evident that the incompetence of the ureteral valve was due to its inflammation.

CASE 3.—*Dilatation due to inflammation (right); dilatation due to obstruction (left).*

A man, aged 59, died of coronary sclerosis. It was known that he had had a carcinoma of the bladder for five years, but the situation of the growth and the patient's condition made operation inadvisable.

Necropsy disclosed a solid, sessile tumor 4 cm. in diameter situated on the base and left posterior wall of the bladder. The left ureteral orifice was obscured at the edge of the growth. There were three smaller implants in the dome of the bladder. Intense cystitis was present. The left ureter and pelvis were enormously dilated, with a capacity of 650 cc. Only a shell of the renal tissue remained. The dilatation of the ureter was notably even throughout.

Fig. 2 (case 3).—Enormous dilatation of the left ureter caused by obstruction.
Irregular dilatation of the right ureter caused by inflammation without obstruction.
The right ureter is on the left of the picture.

Fig. 3 (case 3).—Cross-section of the left ureter (fig. 2); enormous hyper-
trophy of muscle associated with obstructive dilatation may be noted. Infection
was not present; × 38.

The right ureter, however, was not obstructed, and dilatation of its lower half was evident. The dilatation here was not so large as that of the left ureter, and was irregular. The internal diameter of the right ureter varied from 3 to 9.6 mm. At the orifice, the diameter was 4.6 mm. The capacity of the ureter and pelvis was 18 cc. Grossly, there was some injection of the ureteral mucosa (fig. 2).

Microscopic sections from various levels of the obstructed left ureter disclosed enormous development of the musculature (fig. 3). The mucosal and submucosal layers were thinned. Inflammatory reaction was practically absent.

Fig. 4 (case 3).—Cross-section of the right ureter taken from the dilated portion at the same level of the ureter as that in figure 3. There was no muscular hypertrophy, but evidence of inflammation may be noted; × 105.

Sections from the unobstructed right ureter contained muscle that stained poorly, and gave evidence of marked infiltration, with grouped and scattered small round cells and polymorphonuclear leukocytes. In portions, the submucosa appeared edematous. There was no increase of connective tissue in sections of the narrow portion of the right ureter seen in the pyelogram. It is probably more correct to regard such a portion as one in which dilatation had not taken place rather than as a region of stricture.

The different characteristics of these two ureters must indicate a difference in the etiology of the dilatation. On the left was enormous, smooth dilatation, without evidence of infection of the ureter and with marked hypertrophy of ureteral

musculature. At the ureteral orifice was definite cause for obstruction. On the right was a dilatation of more modest extent, and with irregularity of outline. There was no obstruction and in the ureteral wall no muscular hypertrophy, but there were marked inflammatory changes (fig. 4). It was concluded that this was dilatation due to inflammation of the ureteral wall.

CASE 4.—*Infection, the cause of dilated calices.*

A man, aged 75, died of sarcoma of the right axilla with metastasis. Occasional nocturia during the last four years was the only urinary symptom. The urine had contained occasional erythrocytes and pus cells.

At necropsy, very slight enlargement of the prostate gland, of the median bar type, was found. Postmortem pyelograms disclosed apparent clubbing of all calices, without dilatation of the ureters. The capacity of the right pelvis and ureter was 17 cc., and that of the left pelvis and ureter, 15.5 cc. On opening each pelvis, severe inflammation was evident. The ureters gave no evidence of infection, either grossly or microscopically. Inflammation appeared to be the sole cause of the dilatation of these calices. The bladder was normal and gave no evidence of having been seriously obstructed by the prostate gland.

CASE 5.—*Ureteral inflammation.*

A man, aged 62, had been under observation for five years because of diabetes and associated cystitis. Four large vesical diverticula, which did not empty, were known to be present. Five years previously a stone had been removed from the lower part of the left ureter, after four weeks of symptoms. Death resulted from acute renal infection two weeks after the development of symptoms.

At necropsy, left pyonephrosis, with atrophy of the kidney, was noted; the kidney weighed only 100 Gm. The right kidney weighed 250 Gm. Both ureters were dilated, tortuous, sacculated throughout and kinked secondarily. The diameter of the left ureter varied from 3.3 to 12.6 mm., and that of the right ureter, from 3.3 to 8 mm. A small, contracted bladder with severe cystitis and diverticulitis was noted. There were marked injection of the mucosa and some thickening of the ureters and pelves.

Microscopic sections of both ureters disclosed dilated blood vessels, many young connective tissue cells and much infiltration with inflammatory cells. There was no evidence of obstruction of these ureters. There was no trace in the ureter of the former ureterolithotomy. The prostate gland was small, and there had been no obstructive vesical symptoms.

In the absence of obstruction it seems that dilatation of these ureters must have resulted from ascending infection of the ureteral wall with resultant atony.

COMMENT

From analysis of the foregoing cases it seems evident that inflammation is not an uncommon factor in ureteral dilatation. It often acts as a contributory cause, and it may be, in the absence of mechanical obstruction, the only factor in the dilatation. The effect of inflammation on the ureter is conceivably one of interference with function and atony of the ureteral wall, lessening the resistance of the ureter to pressure from within. The dilatation of inflammation has certain characteristics. It is irregular, giving an irregular ureterographic outline. It never reaches the large size often seen with obstruction. The microscopic picture is one of inflammation rather than one of muscular hypertrophy, as is often the case in obstructive dilatation.

That ureteral dilatation always accompanies pregnancy seems to be an established fact. It is generally assumed that the dilatation is due to mechanical obstruction, although the precise manner in which it occurs is not yet clear. Of interest in this connection in this series were two deaths occurring during pregnancy, one in the fourth month and one in the second month. Marked ureteral dilatation was noted in the first case, whereas in the second the ureters were normal grossly and microscopically. It is conceivable that the uterus in the latter case had not reached sufficient size to cause pressure at the pelvic brim, if there is anything in the hypothesis that such pressure causes dilatation.

That the dilatation of pregnancy does not always persist is evident from the fact that in this series six multiparas who had been pregnant from three to eight times had ureters and pelves which were normal grossly and microscopically.

Five multiparas in this series had dilated ureters. Chronic inflammatory changes were evident in the ureters of four on microscopic examination. It seems, then, that the inflammatory changes had prevented the return of the ureter to normal. In the fifth case, in which the ureters were without inflammatory change, a neurogenic origin of the dilatation could not be ruled out.

Many explanations have been offered as to the mechanism of the ureteral dilatation which occurs with prostatic hypertrophy. The truth probably is that no explanation will suffice for all cases.

That it was not due to distortion or kinking of the lower end of the ureter by the enlarged gland was exemplified in case 1. Interference with ureteral emptying by hypertrophy of the vesical wall does not seem a satisfactory explanation (case 1). There were seven cases in which hypertrophy of the vesical wall was marked and in which there was no ureteral dilatation. In two cases in which the vesical wall was thinner than usual the ureters were dilated.

There were twenty-nine cases of prostatic hypertrophy in this series. In twenty of these there was no ureteral dilatation. These ureters were microscopically free from inflammation except in one case, in which acute pyelonephritis was terminal. From the character of the dilatation in certain cases, it is a fair conclusion that inflammation was at least a contributory cause, either by its effect on the ureteral valve or by causing atony of the wall of the ureter.

SUMMARY AND CONCLUSIONS

The diameters of normal ureters may vary within wide limits, both at the widest and at the narrowest points.

The capacity of the normal ureter and pelvis in adults was found to vary from 4.5 to 20 cc. An unusual case in which the capacity was 30 cc. was found.

Ureteral stricture of intrinsic inflammatory origin was not found in this study.

Ureteral spasm may occur soon after death and be evident in postmortem pyelograms.

Dilatation of the ureter can result from inflammation of the wall of the ureter in the absence of mechanical obstruction. Such dilatation presents anatomic and clinical characteristics.

Involvement of the lower part of the ureter in pelvic inflammation, by interfering with ureteral function, may cause dilatation of the upper part of the ureter and renal pelvis, without actual obstruction.

Chronic ureteritis will cause the ureteral dilatation that occurs in pregnancy to persist.

The ureteral dilatation associated with prostatic hypertrophy may have an obstructive cause, although the mechanism is as yet not clear. Ureteral inflammation is frequently a contributing factor and may be the only factor.

CHROMATOPHORE (MYO-EPITHELIAL) TUMORS OF THE MAMMARY GLAND

ARTHUR E. HERTZLER, M.D.

HALSTEAD, KAN.

For more than twenty years I have been acutely sensible of the fact that certain globular cancers of the breast present a particularly bad prognosis. In addition to their external form, they present a varied histologic structure which requires the assumption of a wide latitude of cell metaplasia to keep them within the group of epithelial tumors.

Recently I encountered a patient whose tumor seemed to be a connecting link between the aforementioned group and the intracanalicular fibro-adenomas. As the cells of this tumor seemed to spring from its subepithelial cells, I am calling growths of this type chromatophore tumors, realizing that this is little more than a symbol. Since they do not produce pigment, one cannot call them melanomas, though they duplicate the histologic structure of the pigmented tumors in a striking manner. Amelanotic melanomas would be a more accurate though cumbersome designation.

The use of a term suggesting pigment-producing potentials has a justification in that morphologically the subepithelial cells can be traced from the surface skin down the ducts for varying distances. The epithelium of intracanalicular fibro-adenomas is composed of several layers, and though the lower layer cannot be morphologically proved to have a relationship with the chromatophores of the skin, the clinical course warrants consideration of the possibility of such a relationship. Since so little is known morphologically of chromatophore cells, the failure to demonstrate them about the ducts can have little weight. Perhaps those sufficiently skilled in microtechnic may be able to add something to the knowledge concerning the nature of the subepithelial cells found about the ducts and in the epithelial layers of these tumors. The term "myo-epithelium" has been applied to certain subepithelial cells. Though it is sanctioned by high authority, it seems to assume a hybrid among cells.

At any rate, "myo-epithelium" suggests nothing to the surgeon, while "chromoma" at once calls up the picture I desired to present. Not only does the life history of this tumor resemble the chromomas, but the histologic structure as well closely resembles the varying picture seen in chromomas.

Most surgeons, I believe, are now in the habit of regarding pigmented tumors as forming a class of their own. Certainly nothing in the pathologic literature is more confusing than the attempts which have been made by pathologists to place the pigment-bearing tumors now with the sarcomas and now with the epitheliomas, neither of which they resemble either in morphology or clinical course.

The patient was 49 years of age when she first noticed a tumor in her breast. She had been conscious of its presence for only three months. I believe this observation was correct, for I removed a goiter from her seven years before which resulted in myxedema. In order to study this condition she was kept under close observation, and no tumor was discovered in previous examinations. When she presented herself on Jan. 16, 1931, she had a tumor which was globular, slightly bosselated, densely elastic and freely movable without any attachment at any point.

Fig. 1.—Tumor obtained at the first operation, natural size. Somewhat irregularly spheroidal, it shows slight lobulations with several small cysts. The generally pale pinkish surface is traversed by paler fibrous bands.

It lacked none of the clinical signs of an intracanalicular fibro-adenoma except its appearance late in life and its apparently rapid development.

The first operation, which consisted in the resection of that part of the breast which harbored the tumor, was done on January 17. The tumor, on section, showed indefinite lobulations with here and there small cysts in an otherwise pinkish-white surface (fig. 1). A diagnosis of intracanalicular fibro-adenoma was made in the operating room with but slight misgiving.

The patient returned on September 14, with a large recurrence, and a complete mastectomy was done. The cut surface of this new tumor showed marked cystic formation with a pinkish-white border of varying thickness. The solid part contained some areas of blood infiltration. The tumor still bore gross relations to the intracanalicular fibro-adenomas (fig. 2). The protrusions in the cystic portion were distinctly intracanalicular.

On December 11, the patient returned with a renewed recurrence, which was represented by a number of distinct tumors, of well defined globular outline, movable against their environment and independent of each other. They lacked the
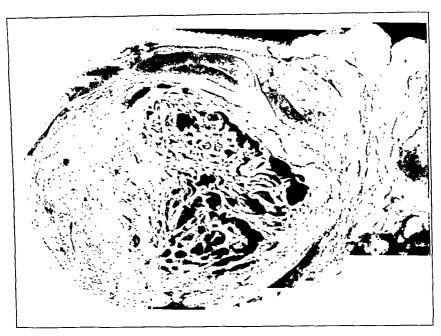
Fig. 2.—Tumor obtained at the second operation, natural size. The left half is made up of pinkish-white areas with here and there some hemorrhagic areas. The right half is made up of a cystic area with trabeculated walls.

Fig. 3.—Second recurrence, natural size. Four distinct tumors, generally expansile in growth, are in evidence. They still retain evidence of the cyst and lobule formation which characterized the primary growth.

hard feel characteristic of epithelial malignant recurrences. On section, these tumors showed a paler pink surface than the preceding recurrence, but were still cystic in parts (fig. 3). The impression these tumors gave on clinical examination, and likewise on section, was that of a recurrent amelanotic melanoma as one sees this in recurrences in tumors of the skin.

The tumor quickly returned, and the patient died on April 19, 1932, fifteen months after the first operation. There was marked local destruction (fig. 4), with extensive metastasis in the axillary and mediastinal lymph glands as well as in the lungs. In the local destruction of tissue as well as in the site and manner of invasion the tumor simulated certain melanotic tumors. The autopsy was done by Dr. C. Alexander Hellwig, who supplied the photograph and tissue.

Histologically, the most interesting phase was the apparent beginning of the malignant growth from cells lying beneath the surface epithelium of the intra-canalicular papillations (fig. 5 A). The part of the primary tumor not involved in the malignant growth was for the most part myxoid in structure with areas
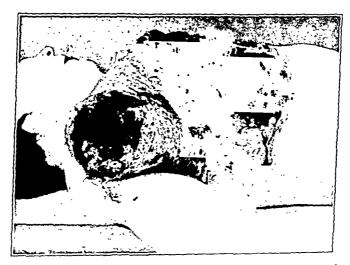
Fig. 4.—Appearance of the tumor area after death. The extensive invasion which the tumor had made is in evidence.

of distinct lipoid structure. The epithelium of the growth was untouched both in the original tumor (fig. 5 B) and in the recurrences (fig. 6). In the primary tumor the cells were spindleform or ovoid. As the rate of growth increased, the cells became more globular and resembled fully the cell forms in the most rapidly growing melanotic tumors. The protoplasm was more or less drawn into prolongations and in most areas presented a poorly staining intercellular stroma (fig. 7). The more rapid the growth, the more irregular the cells became. In the rapidly developing parts of the tumor, cells formed about the lumen of a vessel just as one sees them do in rapidly growing teratomas. as in those of the kidneys and testicles.

Of great interest to me is the fact that a number of eminent pathologists who examined slides from these tumors varied widely in their opinions as to the nature of the growth. These opinions varied from a belief that the growth was unquestioned sarcoma to a belief that it was carcinoma with pronounced metaplasia. When pathologists dis-
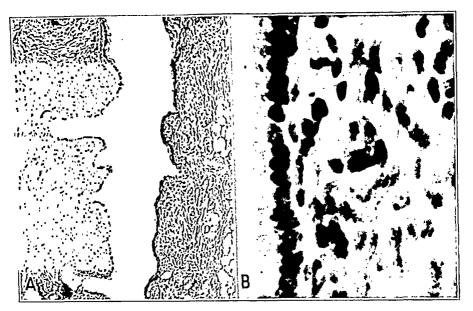
Fig. 5.—Slide from the primary tumor. In *A*, the cells are most numerous just beneath the epithelium. At a greater depth the cells become more spindle-form. In *B*, a high power magnification, the epithelium is shown intact. Beneath the epithelium, the cells are seen to contain large nuclei with many granules.
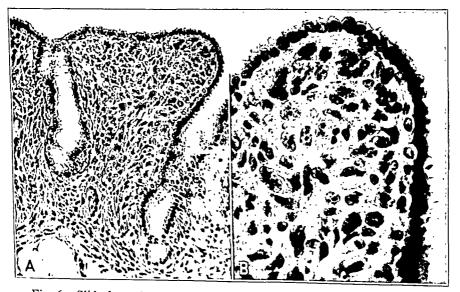

Fig. 6.—Slide from the second recurrence. In *A*, the cells are larger and more deeply staining than in the preceding figure. The surface epithelium forms an untouched and unbroken layer. In *B*, high power magnification, the cells are shown with large granular nuclei.
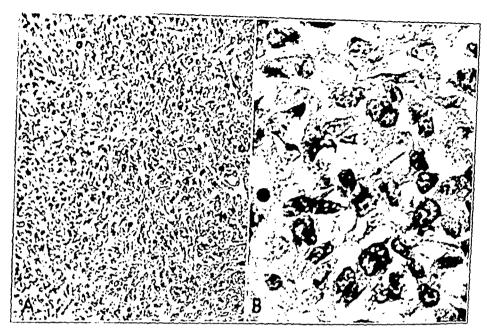
Fig. 7.—Slide from the second recurrence. In *A*, the entire field is made up of a homogeneous cell mass with relatively few small vessels. In *B*, high power magnification, are shown cells of varying forms but the main type is constant.
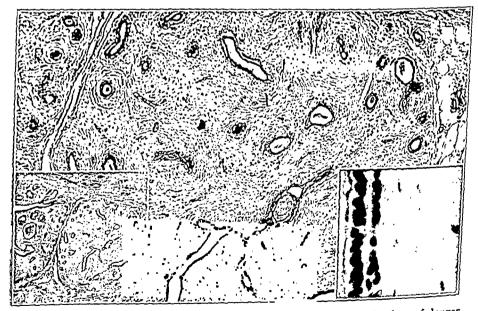
Fig. 8.—Slide from a tiny fibro-epithelioma. The structure is that of larger tumors of this group. The distinct encapsulation of the tumor is shown at the left. The left insert shows the tumor in low magnification; the right, a high power magnification of the epithelium.

agree on the histologic nature of a tumor group, the surgeon is warranted in adopting a classification based on clinical observation which will be useful to him.

As this tumor in its life history reproduces so perfectly, both in its gross manifestations and in its histologic structure, the rapidly growing melanomas of the skin, the provisional classification of this tumor with the melanomas seems to be warranted.[1]

INTRACANALICULAR FIBRO-ADENOMAS

It seems justifiable to interpolate here some observations on the genesis of intracanalicular fibro-adenomas which I have been able to

Fig. 9.—Cross-section of a tumor of the breast, showing pseudo-encapsulation and lobular structure in parts of the tumor.

make in the past. For this purpose the smallest tumors should be selected.

The notable feature is that tumors scarcely larger than a pin's head have the characteristics of large tumors (fig. 8). The epithelium is composed of several layers. The high power photomicrograph (fig. 8, right insert) shows the double layer of cells. It is the lower of these layers from which the tumor here discussed seems to grow.

It is noteworthy that these tiny tumors are perfectly encapsulated and are independent of any other changes in the mammary gland. They

1. This judgment is based on previous studies made on chromomas: Ann. Surg. **60**:89 (July) 1914; **87**:99 (Jan.) 1928; Surgical Pathology of the Skin, Philadelphia, J. B. Lippincott Company, 1931, p. 145.

are found incidentally now and then in the study of normal mammae. It is as near the truth as one can come to assume that in the development of the duct a disturbance in the anlage has occurred, that these tumors represent, in fact, a disturbance in the primary development of

Fig. 10.—Cross-section of recurrence. The tumors are surrounded by a pseudocapsule. The surface shows lobulations with areas tending to cyst formation.
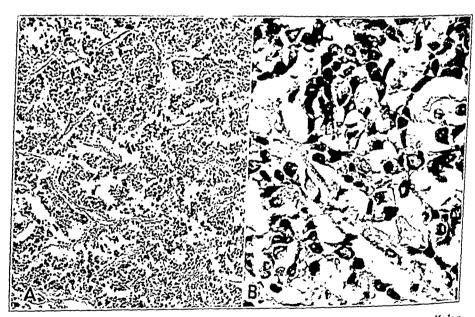

Fig. 11.—Slide from the tumor in figure 10. In *A*, the section is very cellular with irregularly placed stroma. In *B*, the cells vary in size, shape and tinctorial reaction. The stroma is fibroma-like.

the gland. It is not without interest that in the rapidly growing parts of these tumors areas were found which resembled those found in accepted teratomas. The occurrence in the terminal duct is assumed, for in some of them acinus-like areas are found in conjunction with areas showing distinct duct formation.

The case reported here somewhat in detail seems to suggest the possible nature of other spheroidal tumors of the breast which are less obviously related to primary benign tumors, but which run a similar clinical course. They are distinctly spheroidal, suggest an expansile growth by their pseudo-encapsulation, recur as distinct globular tumors, likewise expansile in growth, and are equally vicious in their clinical course. Several such examples may be briefly presented:

A woman, aged 64, first noted a lump in her breast six weeks before consulting a physician. Attention was attracted to the breast because of a slight pain. Four weeks later she had a severe pain in the armpit. A firm tumor the size of an egg, which the patient had not discovered, was palpable in the outer upper quadrant of

Fig. 12.—Cross-section of a large pseudo-encapsulated tumor of the breast with lobulation and cyst formation.

the left breast. Large glands were palpable in the axilla. Radical operation was performed.

On section, the tumor was seen to be spheroidal with a well marked pseudo-capsule in some areas. The pale pink surface showed pseudolobulations (fig. 9).

Eight months after operation the growth recurred. It was removed (fig. 10). The main tumor was the size of a lemon, and there was a smaller one the size of a walnut. The cut surfaces presented the same picture as the primary tumor. Both had a pseudocapsule.

The microscopic structure was cellular, resembling t̄ testis (fig. 11 *A*). The cells were irregular in size, fo (fig. 11 *B*). There was some fibrin-like intercellular s melanotic tumors, particularly in the young, sometimes sh

A woman, aged 51, a year before she sought medical ad tumor the size of a marble. A spheroidal slightly bossela

of an orange was palpable. The skin was attached to the tumor, but there was no dimpling or retraction of the nipple. The cross-section showed a pseudo-encapsulated tumor, the surface of which showed indications of lobulation and in parts a tendency to cyst formation (fig. 12).

The slide showed spheroidal masses of cells with degenerated areas between them. The cells were of varying size, as were the nuclei. The striking feature was the large number of cells with a large amount of clear cytoplasm. These suggested the clear cells sometimes seen in the ducts of normal breasts.

The structure of the last mentioned tumor resembled that in the first case. Its origin from a primarily benign tumor cannot be proved, but when first discovered the patient compared it in size and shape to a marble. The tumor resembled that in the first case to such a degree that such a possibility must be entertained.

It has been my experience that the malignant tumors of the mammary gland which possess a pseudocapsule, in whole or in part, always terminate fatally within a year or two, no matter how soon after the discovery of the tumor operation is performed, or what the extent of the operation, or whether or not there are palpable metastases. These tumors occur in women at the menopause or beyond that period. I have not observed them in younger women. My youngest patient, operated on some twenty years ago, was 46 years of age.

There is a group of tumors which begin within the acini and in which the cells are loosely joined and diffusely scattered. Some of these appear as though they might have arisen from the subepithelial cells, but instead of growing away from the lumen of the acini they grow into it. At any rate, many of these tumors are globular, though they do not develop a pseudocapsule, and their course is usually malignant.

CONCLUSIONS

1. Intracanalicular fibro-adenomas may give rise to malignant tumors which spring from the subepithelial layer.

2. They run a course parallel with that of the chromatophore tumors in the skin.

3. Globular pseudo-encapsulated cancers of undemonstrable origin run a similar clinical course.

4. These tumors like melanotic tumors do not cause metastases to the bone.

A NEW METHOD OF RECONSTRUCTION OF THE LIP

GEORGE WARREN PIERCE, M.D.

AND

GERALD BROWN O'CONNOR, M.D.

SAN FRANCISCO

Successful reconstruction of a lip is a difficult and intriguing problem. The addition of a new operation to the remarkably long list of operations proposed in the past can be justified only if the new procedure proves to possess added advantages and fewer disadvantages than its predecessors. In reviewing the literature, about sixty-five different methods for this operation were discovered, and this new procedure is described because it possesses the advantages of simplicity, cosmetic fidelity to the normal in its results, noninterference with muscle and nerve supply and production of nearly normal function, and is applicable to restoration of either the upper or the lower lip.

Before this problem can be successfully adjudged, its factors must be analyzed, and the obvious first step is a review of the anatomic structures about the mouth together with their physiologic action. Of these structures, the musculature is the most pertinent to our problem. The motor innervation and the blood supply are next in importance. The following is a description taken from Deaver's "Surgical Anatomy." [1]

The muscles of the mouth are the orbicularis oris, the levator labii superioris, the levator anguli oris, the zygomaticus major, the zygomaticus minor, the buccinator, the risorius, the depressor labii inferioris, the depressor anguli oris and the levator labii inferioris.

The orbicularis oris muscle (sphincter oris), nearly an inch in breadth, surrounds the mouth, forming a sphincter; at its periphery it unites with several muscles which act upon that aperture. It consists of two parts—an inner, central, or labial part, and an outer peripheral, or facial part; the two differing in appearance and in the arrangement of fibers, like the orbicularis palpebrarum muscle. The inner, central, or labial portion consists of pale, thin fibers, fine in texture, corresponds in position with the red margin of the lips, and has no bony attachment, but is continuous around the angles of the mouth from one lip to the other. The outer, peripheral, or facial part is thinner and wider than the labial, and has a bony attachment as well as connection with the adjacent muscles. In the upper lip

1. Deaver: Surgical Anatomy, Philadelphia, P. Blakiston's Son & Co., 1901, vol. 1, pp. 498 and 499.

the orbicularis oris muscle is attached at each side of the middle line to the lower part of the septum nasi by the naso-labial slips, and to the alveolar border of the upper jaw opposite the incisor teeth; in the lower lip it is attached to the alveolar border of the lower jaw opposite the canine teeth by a single fasciculus (musculi incisivi). The cutaneous surface of the muscle is intimately connected with the skin of the lips and surrounding parts. The intimacy of this union is so great in some instances that the mouth is surrounded by radiating wrinkles, especially marked in the upper lips of women. The labial integument of the male probably
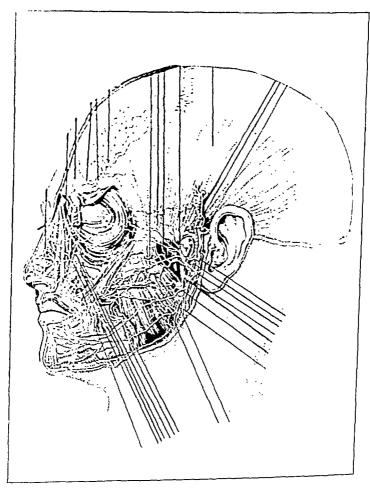
Fig. 1.—Anatomy of the face. Note the musculature and the nerve supply about the mouth. (From Deaver: Surgical Anatomy, Philadelphia, P. Blakiston's Son & Co., 1901.)

contains fewer wrinkles on account of the presence of large hair bulbs. The deep surface of the orbicularis oris is covered by mucous membrane, between which and the muscle, in the submucous tissue, are the coronary arteries and the labial glands.

Nerve Supply.—From the buccal and supra-maxillary branches of the cervico-facial division of the facial nerve.

Action.—When the facial and labial portions act conjointly, they press together and project the lips. The labial fibers acting alone bring the lips and the angles

of the mouth together and invert the lips. The facial fibers acting alone press the lips against the alveolar borders of the jaws, and, at the same time, evert the lips. The orbicularis oris is the antagonist of all those muscles which converge to the lips from the various parts of the face.

Of prime importance is the orbicularis oris with its sphincter action. All the other muscles about the mouth are opposed to this muscle. This sphincter action must be kept constantly in mind together with the axiom that a sphincter cut at one point still functions as a sphincter, but cut at more than one point, loses its function.

One only too frequently notes in examining patients for whom reconstruction of the lower lip has been done (usually after the removal of a new growth) that the new lip is short and tense and the upper lip is forced into protrusion; indeed, there is almost a Gumpian expression. Functionally, such a lip is a constant distress, for there is usually continual drooling of saliva, and clarity of speech is markedly disturbed. It is most difficult for these people to sound *b, f, m, p, v, w, ph,* and *wh.* The great number of operations devised for the repair of the lip indicates that no method gives completely satisfactory results. Indeed, many methods fall far short of even a reasonable repair.

REVIEW OF OPERATIVE METHODS

A study of these many operations is illuminating for the development of rationale of procedure, and in many cases the factors contributing to the failure to approach good cosmetic and functional results are obvious.

Among the early operations, Chopart, in 1785, designed an advancing flap from the chin by carrying parallel incisions downward to the neck, making a square flap pedicled below. This flap was undermined and advanced upward to fill the defect. The first and most obvious criticism of this method is that no epithelial lining has been provided for the oral side of the flap. The sine qua non of reconstruction involving any body cavity is that an epithelial lining as well as covering must be provided. Alquié, in 1855, modified Chopart's operation by adding flaps of mucous membrane from the cheeks. Other disadvantages are the tendency of the flap to be pulled down and to contract; also muscular control is limited, and the nerve supply to the muscles of the lower lip is cut. Serre used horizontal advancing flaps, one from each cheek, but this resulted in a short tight lip. Zeiss employed double vertical flaps pedicled below. Lisfranc devised an operation with a median line vertical incision and two lateral incisions, and Sédillot used lateral incisions with supplementary incisions into the upper lip to allow a borrowing of tissue to form the angles of the mouth. Beau made two outward and downward curving incisions from a central point and rotated the flaps upward.

Weber employed horizontal overlapping flaps below the defect, and the flaps were then slid one upon the other so that the tip of one flap approximated the base of the other. Dieffenbach and also Adelmann used lateral angled flaps. Juselre and also Reid carried their incisions from the angles of the mouth outward and downward and then rotated the flaps inward. Pollosson's operation and Berger's were similar in the use of lateral horizontal incisions and shifting flaps. Nélaton and Ombrédanne devised a bold procedure. An incision was carried back from the angle of the mouth to the ear and thence downward and for-
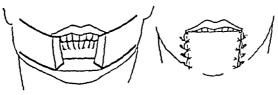
Fig. 2.—Advancing type of flaps.

Fig. 3.—Advancing overlapping type of flaps.

Fig. 4.—Transferred flap type.

ward beneath the mandible. The cheek was taken full thickness to the anterior border of the masseter muscle and subcutaneously thence to the ear. The whole flap was moved medially to fill the defect. Auger used a large, low and lateral pedicled flap, and Ledrau and Berg used smaller single inferior lateral shifting flaps. Viguine-Morgan, Wölfler, Mazzoni and others employed a large double pedicled flap embracing most of the lower part of the face and chin.

A number of surgeons conceived the principle of the use of a buttress of tissue on the chin to support the newly formed lower lip. In this manner, Sédillot turned two symmetrical vertical flaps pedicled above and buttressed them on the chin. Lallemand's operation consisted of a

transposed flap taken low down and pedicled at the side, and this plan followed Langenbeck, both using buttress tissue on the chin. Landreau used a single recurving flap. The Trélat and Buchanan and Syme's operations employed lateral advancing flaps but left a portion of chin tissue for buttress. Morestin's operation swung up a double pedicled flap from beneath the chin to rest on the normally anchored tissue. Grant extended long incisions outward from the angles of the mouth, dissected the upper flaps free and swung them to the midline. Larger's operation commanded considerable attention in the employment of an advancing flap including the outer third of one side of the upper lip and extending out into the cheek. Bruns swung down two full thickness ascending lateral flaps. Watts reported a reconstruction of the lower lip with a flap from the arm, the raw surface of which had been grafted and healed before the transfer of the flap. This has the disadvantage of skin of different color and texture and the discomfort of having the arm maintained against the face for a period of two weeks.

Fig. 5.—Buttress type of operation.

Hoffmann, Morestin, Evans, Duformentel, de Francesco, von Mutschenbacker and Twyman offer various types of advancing flaps. Joseph uses rotating pedicled flaps. Tzaïco brings up long cervical reverse flaps from the midline, while Sebileau employs temporal pedicle flaps. Esser devised an operation with ascending triangular pedicles which were brought down and fitted to form a quadrilateral, and he has also introduced a bold figure 3 incision, which involves most of the cheek and upper half of the neck, and which is rotated into the defect.

Sir Harold Gillies, in his war reconstruction work, designed numerous ascending and descending flaps, and his results were uniformly the best of all those reviewed. Pickerill favors a temporal pedicle flap joined to a neck flap for lining and thence referred to the defect.

A review of all these operations demands a measurement of each by the yardsticks of simplicity, conservation, function and cosmetic result, for too many of the plans fall short on one or more counts. Analysis and criticism again demand reference to the basic anatomy and physiology of the part. Advancing flaps are only occasionally used in modern reconstruction surgery on account of the tension and the distortion produced. They are not adequate, and experience teaches that they almost always fall short of producing even a fairly good result.

This point is stressed now with especial emphasis, because books on surgery are replete with diagrams of many varieties of flaps for the correction of defects of the lips and show handsomely completed operations (diagrammatically) as cosmetically perfect. This we know to be scarcely possible from trial and from logical deduction based on the fundamentals.

The older methods nearly all failed to provide an epithelial lining, but in recent years no operation is planned without strict attention to this factor. A common fault of most operators, unless they have been trained in reconstruction surgery, is to underestimate persistently the size of the defect to be repaired and to fail in judgment of the amount of tissue requisite to accomplish the repair, or to be too sanguine of the possibility that the flap may be properly mobilized for the consummation of the transfer. These difficulties constantly menace such plastic procedures and give added strength to the plea for simplicity of plan. Then, too, a properly planned operation will obviate the terrific and unnatural distortion of the donor part which follows the adoption of many of the reviewed recommendations, for lack of balance of facial contour is certain to result in dismay for the surgeon and dissatisfaction on the part of the patient. Once again, the object of the operation is not merely the closure of a defect, but in addition the satisfaction of all the foregoing factors.

Further, judgment dictates due regard for normal lines of tension of the skin, and this Larger has shown graphically in his diagrams of his lines of tension. A study of these diagrams will reveal the fact that flaps can be selected to fall within these lines and that failure to do this militates against the best results. Hunt quoted Larger in his statement, "If due regard is shown for these lines and incisions are made in their direction, inconspicuous scarring is usually the result. Any incision made at right angles to these lines, however, results in scar formation." In addition, if the natural grooves are followed, the scarring is even more inconspicuous. A contemplation of these factors suggests the nasolabial groove as the optimum site for the appropriation of tissue.

Distortion of the mouth after reconstruction by many of the methods enumerated is strikingly evident. This is true especially of flaps taken from one side, because such technic creates marked tension on one side as against relaxation on the other with consequent unbalancing of the facial contour. Moreover, there may be added to this distortion the atony and sagging caused by severed muscles or by lost motor nerve supply to the muscles of that side. Other methods of this type cause a shortening of the oral commissure on the side of the flap. This lack of symmetry gives the patient an unnatural and bizarre expression. Advancing flaps are especially undesirable, as they not only distort the surrounding tissue but furnish insufficient material for a full everted

lip and consistently produce the shortness and tenseness which mars the completed reconstruction. The short, tight lower lip not only commonly causes drooling but also an abnormal protrusion of the upper lip beyond the lower and interferes seriously with the clarity of speech.

A selection of flaps through the full thickness of the face is a grave mistake. If such a plan is adopted, the incisions are made through the integrity of the sphincter of the mouth, thus destroying all possibility of proper function. Inclusion of this transposed muscle, while technically completing the normal constituents of the lip, defeats the functional power of the part. Only recently the fallacy that inert muscle can be of functional value was illustrated by the report of a case in which a strip of sternomastoid muscle was utilized and implanted into the reconstructed lip.

Again, scrutiny of the anatomy of the face will recall that innervation of the muscles about the mouth is derived from the branches of the facial nerve. Diagrammatically, the branch to the muscles of the upper part of the mouth come from the nerve trunk which crosses the face approximately in a line from the lobe of the ear to the middle of the upper lip. The muscles of the lower lip and chin are innervated by a branch extending approximately in a line from the lobe of the ear to the middle of the chin. It is therefore evident that many of the flaps suggested not only will destroy the integrity of the indispensable facial musculature but will render the remaining musculature impotent by the destruction of its motor stimulus.

Profiting by the careful analysis of all the factors of the problem of reconstruction of the lips and forewarned by the unsound theories of such reconstruction which have resulted unsatisfactorily, we offer the following operation as a basic procedure for the reconstruction of either the upper or the lower lip. This operation possesses the necessary qualifications before mentioned of simplicity, cosmetic fidelity to the normal in its results, production of nearly normal function and non-interference with muscle and nerve supply.

TECHNIC

The principle of the operation is the use of two full length opposed ascending flaps placed in the nasolabial groove. The technic of the operation is shown in the accompanying diagrams and pictures of the patient before and after operation. These flaps consist of skin and subcutaneous tissue only, and at no point is any part of the musculature or its motor nerve supply severed. The nasolabial groove was selected as the donor site, because scarring there is inconspicuous and especially because this region provides a sufficient supply of facial tissue which is relatively free from hair. Furthermore, this tissue will be the same color and texture as the normal lip, which is a strong argument for its use, rather than flaps taken from distant parts. The skin of the face is distinctly different in texture and color from that of any other part of the body. Flaps taken from the arm and chest stand out with startling prominence on account of these differences,

and while such flaps may furnish sufficiency of normal tissue, the cosmetic result is not pleasing. It will be seen that our flaps are placed according to the principles of "Langer's lines of tension." The flap from one side is brought down and reversed to form the lining of the lip in such a manner that the skin surface is toward the mouth and the raw surface is directly outward. It is then sutured into position after splitting the margin of the defect so that raw surface will come in contact with raw surface, and the skin surface of the flap will be in continuity with the mucous membrane of the mouth. The opposing flap is then brought down to furnish the covering and is sutured raw surface to raw surface and the lining flap sutured to the free skin edge of the facial wound.

Mindful of the principle of the sphincter action of the M. orbicularis oris, these opposing flaps form the bridge between the two ends of the severed orbicularis oris muscle and reconstitute its function as a sphincter muscle. The adoption of this principle obviates the necessity of the employment of any transplant musculature, as it performs better in this manner than with the unnatural function of a transposed muscle or uninnervated muscle. All the opposing muscles may act normally as they are anchored into the base of the new lip.

The blood supply is naturally adapted to these flaps, as the bases of the flaps lie over the facial arteries with their coronary branches, and thus the vitality of the flaps is almost certainly assured.

In the illustrated operation, when these flaps were brought down into position, as shown in the accompanying photographs, smaller flaps of mucous membrane were taken from the lateral borders of the defect and blended into the superior border of the sutured flaps in such a manner as to form the angles of the mouth and a goodly portion of the vermilion border of the lip. These mucous membrane flaps were carried upward, so that their bases approximated the normal angles of the mouth. A further transposition of mucous membrane from the upper lip was planned to complete the vermilion border of the lower lip, but, as was noted by Sir Harold Gillies in his reconstruction work during the war, flaps of skin turned into the mouth were found to take on the appearance and characteristics of mucous membrane. We found that the remainder of the border of the skin forming the upper margin of the lip and not covered by mucous membrane took on these characteristics to such a degree that a well developed simulation of the normal vermilion border took place and close examination is required before the difference can be detected. Such transplantation of mucous membrane is relatively easily effected. The patient is thoroughly satisfied with the appearance of the lip and does not wish to have further transposition of the mucous membrane done.

After two weeks the bases of the pedicles are returned, and then a period of from two to three months should elapse before final retouching of the newly formed lip is done. These long full length flaps have an added advantage as they do away with all the troubles which come from the joining of bilateral flaps in the midline, at which point the suture line is apt to break down and contraction is apt to occur; also the scar at this point is a cosmetic disfigurement. Minimal scars on the face will be noted in the accompanying photographs of the finished case, as these photographic prints are from unretouched negatives made by us. A further advantage of the full length flap is the certainty of sufficiency of tissue since the defect can be accurately measured and the flaps appropriately fashioned. Sufficiency of tissue avoids the too common short and tense reconstructed lip.

The criticism might be voiced that this method is not readily applicable for immediate repair of a lip defect (as following the removal of the part on account of a new growth). It is true that the repair is better done after healing is complete than when attempted with the tissue
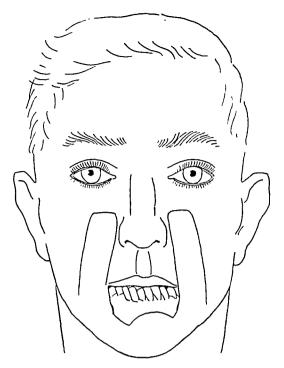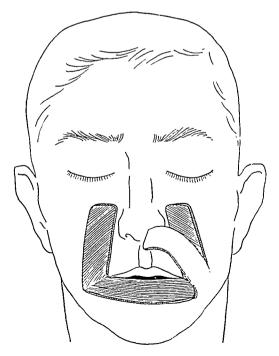
Fig 6.—The flaps are outlined.

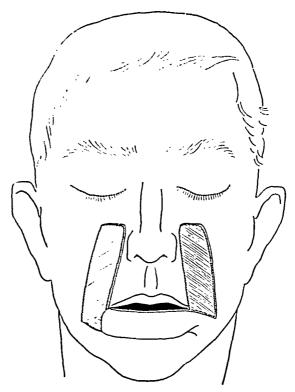Fig. 7.—One flap is brought down and reversed to form the lining.

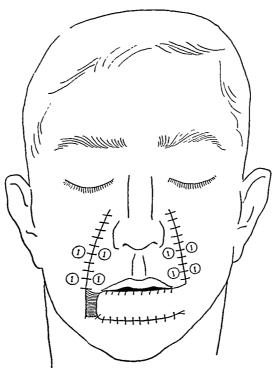Fig. 8.—The other flap is brought down to form the covering.

Fig. 9.—The suturing is completed. Mattress sutures of silkworm gut through buttons relieve the tension on the cheek wounds.

in the region of the bases of the pedicles in an edematous and perhaps infected state. Such a condition would jeopardize the blood supply of the flaps by the mechanical effect of pressure and by favoring thrombosis of the vessels. It is far better to allow the patient the discomfort of a few weeks or months without a lip than to sentence him to a lifetime of discomfort and social limitation by the over-zealous efforts to "fill the gap." Then, too, surgical judgment dictates a waiting period after removal of new growth tissue until a reasonable certainty exists that there will be no recurrence of the tumor.

The cosmetic result can be judged by the reader. Special attention is called to the ease of closure of the mouth and to the profile views

Fig. 10.—Condition of the patient before operation.

with the normal-appearing groove between the chin and lower lip. There may be a few hairs on the base of the inturned flap, but these can be readily and permanently removed by the electric needle. Attention is also called to the photographs illustrating the function and ease with which the patient opens his mouth and shows his teeth. The action of showing the teeth indicates efficient anchorage of the radiating opposing muscles. In the last picture the patient is shown whistling, an accomplishment with the new lip which he has only recently developed, following the gradual softening of the transplanted tissues. This illustrates the sphincter action obtained in the orbicularis oris muscle and the soundness of the principle of bridging the divided ends of this muscle.

REPORT OF A CASE

H. W., was first seen by us on Jan. 27, 1930. His complaint was total loss of the lower lip from cancer. The full history is not given, since the salient features are the only ones germane to this paper. The patient was 47 years of age at the time of his first visit and had always been in good health with the exception of measles at the age of 9 years, to which there were no sequelae.

Seven years before we saw him he noted a "crack" in the mucous membrane of the lower lip. This persisted, but finally healed, then broke open several times. A "lump" eventually developed at the site of the "crack," and this was treated by roentgen rays. The tumor did not disappear and was excised surgically in November, 1928. Microscopic examination of the tissue revealed basal cell epithelioma. The tumor recurred and was removed by electrocautery on Jan. 17, 1929.
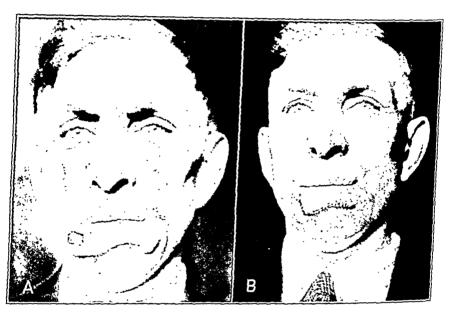

Fig. 11.—A, condition of the patient after healing of the transposed flaps. B, the bases of the pedicles are returned; the suture material is in situ.

The patient had been a heavy smoker, using a pipe and cigarets.

When we saw him first on Jan. 27, 1930, he presented a complete loss of the lower lip. No induration was present, and no glands were palpable in the neck. The wound had been healed one year. The Wassermann test in the blood was negative. His condition on his first visit is shown in figure 10.

Reconstruction was started on March 21, 1930. At the first operation, which was done with the patient under ether anesthesia, the ascending flaps were fashioned (fig. 6), brought down and sutured into the defect, after splitting the margins of the defect. The lining flap was placed skin surface in, as shown in figure 7, and the covering flap was brought over as in figure 8. Small flaps of mucous membrane were turned up from the lateral borders of the defect to form the angles of the mouth. Mattress sutures of silkworm gut, passed through buttons, relieved tension on the skin of the cheek wound, and the completed operation is shown in figure 9. Horsehair was used for skin closure. The healed condition of this stage is shown in figure 11 A. Readjustment of the pedicle bases was done April 10, 1930, under
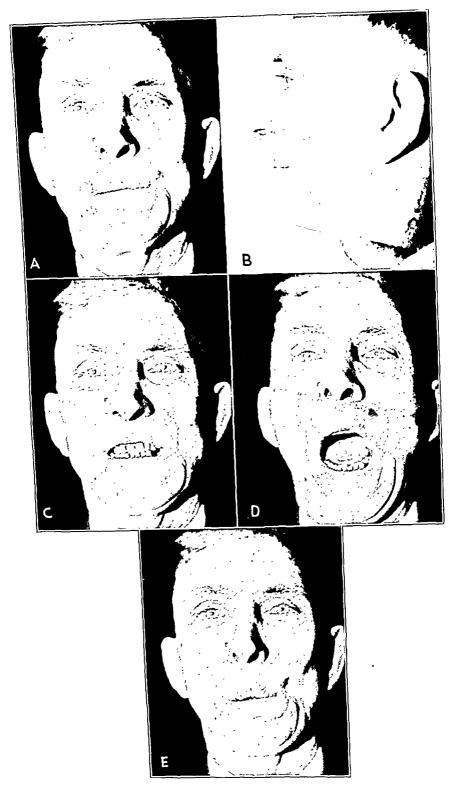
Fig. 12.—*A*, the result of the operation. There is no distortion of the lip or face. *B*, the profile view shows the full contour of the reconstructed lip and the normal approximation with the upper lip. *C*, note the action of the radiating muscles opposing the M. orbicularis oris. *D*, the ease of opening the mouth is shown. *E*, the patient is shown whistling. This illustrates the action of the orbicularis oris muscle through the bridge of the transplanted flaps.

local anesthesia, procaine hydrochloride 1.5 per cent, and the result is shown with the suture material in situ in figure 11 B. Two small readjustments have been made since then, and the final result is shown in figure 12.

CONCLUSION

We must return to the statement of requirements laid down in the first paragraph and measure the result obtained in this case by the yardsticks of the declared essentials. Thus:

1. Simplicity. Few operations of this type offer as simple technic, and this simplicity is evident from the drawings.

2. Cosmetic fidelity to normal. We would be rash indeed to compare our results to Nature's handiwork, but we surely should not cease in our attempts to duplicate her art, and a reference to the photographs will show that the contours of the reconstructed lip do approach the outlines of the normal.

3. Noninterference with muscle and nerve supply. It is evident that there is no interference with either muscle or nerve supply, as the flaps are taken through skin and superficial fascia only.

4. Near normal function. Again we cannot duplicate Nature, but the final photographs do show that, for the ordinary movements, this lip is a functional entity.

5. The method is applicable to restoration of either the upper or the lower lip. The upper lip may be constructed in this manner by planning the bases of the flaps to lie at a point in a line with the proposed lip.

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CHYLE CYSTS OF THE MESENTERY

ARTHUR N. COLLINS, M.D.

AND

GEORGE L. BERDEZ, M.D.

DULUTH, MINN.

Porter[1] presented the subject of chyle cysts of the mesentery before the Western Surgical Association twenty-six years ago. He reported a case of his own and discussed 20 cases, reports of which had appeared in the literature. He regarded the chyle cyst as a surgical rarity, and believed that it was less common than the serous mesenteric cyst. On examining the records of autopsies at the University of Minnesota recently, we found that in approximately 15,000 autopsies no case of chyle cyst had been recorded. In a search of the clinical records of St. Luke's and of St. Mary's hospitals, Duluth, representing a total of over 200,000 cases, we found that but 2 cases of chyle cyst had been recorded. In the Los Angeles General Hospital, according to Alesen,[2] no such case was recorded from 1912 to 1929.

Friend[3] assembled 52 instances from 1875 to 1912; Benedict[4] included Friend's list and collected a total of 96. Flynn regarded mesenteric tumors as among the rarest of those in the abdomen. The consensus of these men seems to be that approximately 200 cases might be found in medical literature.

REPORT OF CASES

The 2 cases we wish to report are as follows:

CASE 1.—A boy, aged 4, was referred to one of us by Dr. Grover on Dec. 5, 1930. Two years before the child had been operated on for appendicitis, but drainage had not been employed. The symptoms at that time were similar to those for which the child was referred. The present attack began with acute pain at about 2 o'clock in the morning of December 4. The mother gave an enema with some result, and the child vomited. A second enema, because of the continuance of pain, brought no result. She called her physician on December 5. The history of appendectomy and the nature of the symptoms prompted the physician to suspect intestinal obstruction, and he sent the boy to the hospital, where Dr. Doolittle saw him in consultation. The following report was made: The leg was flexed,

1. Porter, M. F.: Chylous Cysts of the Mesentery, Tr. West. S. A., 1905, p. 242.

2. Alesen, L. A.: Chylous Cyst of the Mesentery, California & West. Med. 30:261 (April) 1928.

3. Friend, E.: Mesenteric Chyle Cyst, Surg., Gynec. & Obst. 15:1 (July) 1912.

4. Benedict, A. L.: Bibliography of Chylous Cyst of the Mesentery, Surg., Gynec. & Obst. 16:606 (June) 1913.

and the facies anxious. There were dark circles under the eyes. The tongue was dry and coated, and the breath fetid; the tonsils were clean but red; there was no postnasal exudation. The ear drums showed some luster. There was slight enlargement of the glands. The lungs were normal, and no murmurs were heard in the heart. The pulse was 100 and regular, and the temperature, 101 F. The abdomen was slightly distended (oval) with slight definite fulness in the extreme lower right quadrant. Marked tenderness and spasm were noted over the entire abdomen, with the maximal findings over the lower portion of the right side of the abdomen, which was too tense for one to palpate any

Fig. 1.—Specimen photographed a few hours after autopsy. C is the largest of the cysts. Other smaller cysts are grouped around the intestinal margin.

masses. There were no lumbar spasms. Definite flatness was noted over the hypogastric and iliac regions, and there was considerable pain in the abdomen at times.

Rectal examination revealed some indurated bogginess of tissue in the lower portion of the right side of the abdomen. No definite accumulating mass was felt. The hemoglobin was 85 per cent; the red cell count, 4,580,000; the white cell count, 25,900, and polymorphonuclears, 92 per cent. Roentgen examination with an enema of barium sulphate under fluoroscopic control showed that the opaque solution passed all the way up the colon and into the terminal ileum. There was no roentgen evidence of diverticuli, a new growth or intussusception. With the

history of the sudden onset of the attack of abdominal pain and vomiting and in consideration of the foregoing findings, operation was advised at once but no definite diagnosis was made.

When the abdomen was opened, a milky, odorless fluid escaped from the peritoneum. A hard nodular mass was found below the level of the umbilicus, semilunar in shape and running transversely in the lower portion of the abdomen. The mass was delivered and found to be in the mesentery of the small intestine. It consisted of small, pure white masses, some clear cystic masses and several apparently hemorrhagic ones. The total mass was so extensive, involving so much of the

Fig. 2.—Specimen showing the opposite side from that in figure 1.

mesentery, that no attempt at resection was made. Smears and culture were taken at the time. These showed diplococci and were reported later as pneumococci. The boy lived four days; extreme distention developed, and he died of peritonitis.

Autopsy, which was performed a few hours after death, showed: (1) chylangioma of the mesentery with formation of multiple cysts, (2) status after an old appendectomy, (3) pneumococcus peritonitis, (4) edema and congestion of the lungs, (5) beginning bronchopneumonia of the right lung and (6) status after a recent laparotomy (exploratory).

The upper loop of the intestine was extremely distended, measuring up to 14 cm. in circumference (fig. 1). The serosa of the distended intestine was congested

Fig. 3.—Microscopic section from the cystic area: *A*, thin-walled dilated lymphatic spaces; *B*, larger lymphatic with thin layer of the fibrous connective tissue beneath the lining epithelium; *C*, clumps of lymphocytes and coagulated albuminous material.

and showed numerous small hemorrhages. There were no signs of mechanical obstruction of the intestine. Superficial ulcerations of the valvulae conniventes of the small intestine were seen. It was noted that there were no dilated chyliferous vessels in the serosa of the small intestine or in the mucosa, not even in that segment connected with the cystic mesentery. The retroperitoneal glands were somewhat edematous. The thoracic duct was of normal size and contained a small amount of slightly cloudy fluid. The part of the mesentery showing the cystic changes corresponded to a loop of the small intestine 10 inches (25.4 cm.) in length and beginning about 2 feet (60.96 cm.) below the end of the duodenum (fig. 2). Here the mesentery was thickened and showed cystic formations, some watery in appearance, some bluish and some milky. A few of the cysts contained hemorrhagic serous fluid. The largest of the cysts measured 8 by 4.5 by 3.4 cm. This was irregular in shape and was multiloculated. There were numerous other cysts measuring from 1.5 to 2.6 cm. in diameter, and many much smaller. Some of the cysts near the margin of the small intestine involved the serous and muscular coats of the small intestine. When the mass had been cut through, the cut section gave a cavernous appearance. Some of the cystic nodules which had a more compact consistence showed on the cut surface cavernous spaces filled with clotted blood (fig. 3). Small lymphatic glands and lymphatic nodules included in the tissue between the dilated lymph spaces showed moderate dilatation of their sinuses, especially of their peripheral sinuses. These dilated sinuses contained lymphocytic cells and larger mononucleated cells. Small lymph glands taken from the involved mesentery showed similar changes, while glands from the mesentery farther away showed a more normal condition. No truly solid tumor mass could be found. An irregular network of whitish channels of varying thickness was seen in places; these were filled with milky fluid. One larger cystic space near the root of the mesentery contained more compact fatty masses resembling caseated material but more whitish. Microscopically, this was formed chiefly of fat droplets of irregular sizes. Smears from the peritoneal exudate showed pneumococci.

The second case we are recording through the courtesy of Dr. W. A. Coventry, who collaborated with the late Dr. T. R. Martin in its study. This case was more chronic.

CASE 2.—A woman, aged 48, for five months complained of burning in the epigastrium and vomiting after meals which sometimes caused her to leave the table. She felt better if she kept very quiet and also if the stomach was empty. The appetite was poor, but the bowel movements were regular and at times a little loose. She tired easily and complained of nervous chills. She had had one stillborn child seven years before. She stated that she had always had "weak blood." There was a past history of typhoid. She was a frail, thin woman, weighing 95 pounds (43.1 Kg.). Her blood pressure registered 150 systolic and 90 diastolic. The hemoglobin was 46 and the red cell count, 3,880,000. The temperature was 98.2 F. The urine was normal. The Wassermann reaction of the blood was negative. In the lower left abdominal quadrant close to the abdominal wall was felt a tumor the size of a chicken egg. The enema of barium sulphate gave negative results except that pulling on the tumor seemed to drag the sigmoid with it. The diagnostic impression was that the condition was either a tumor of the sigmoid or an enlarged mesenteric gland.

At operation Dr. Coventry found a large number of tumors in the mesentery of the small intestine running up to the root. Some of these appeared caseous and some cystic. Some were as large as an egg. The involvement was too great for resection. The patient failed and died on the seventeenth day. At autopsy, numerous thin-walled and thick-walled cystic tumors, the size of an English walnut and smaller, were found at the base of the mesentery.

A larger tumor measuring 8 by 8 cm. in diameter was found; it was composed of a conglomeration of mesenteric and peritoneal lymph glands. Several cystic tumors were in intimate contact with the wall of the intestine and were apparently connected with the subserous, dilated, chylous vessels of the small intestine. The large tumors at the base of the mesentery were surrounded by an edematous area. Some cavities were filled with puslike greenish-yellow material. The walls of these were especially edematous. The mesenteric glands were edematous throughout and were often connected more or less intimately with the cystic formations. The small intestine was irregularly dilated. The wall of the small intestine was irregularly thickened in places. The serosa was much thickened and was congested, and a few dilated and distended subserous chylous vessels could be seen. The mucosa of the small intestine was edematous in places and showed numerous small hemorrhages. Here and there, small chylous cysts could be seen. The small intestine could not be separated from the mesentery without opening of several of the cysts described. The thoracic part of the thoracic duct was slightly dilated and filled with a watery content. The larger lymphatics along the primary iliac vessels were slightly dilated. The cisterna chyli was involved in the tumors formed by the conglomerated glands at the base of the mesentery and could not be found.

Microscopic examination showed the largest gland at the base of the mesentery to contain in its cavity many leukocytic cells, lymphatic cells, a fibrinous network and very numerous, often intracellular fat droplets of varying size. The wall of the cavity was formed by granulation tissue with many fibroblasts and plasma cells; the fibroblasts were often loaded with fat droplets. In the wall of the cavity the lymphadenoid tissue was still well preserved, and some of the dilated sinuses were filled with desquamated endothelial cells loaded with fat granules. Other cysts showed the same structure. The wall of the cyst was formed by connective tissue, which was infiltrated with many lymphocytic cells.

COMMENT

Friend,[3] in 1912, studied a group of 52 cases and found that these cysts may occur at any age from early childhood to late in life. There is no particular age at which one may look for them. He, and also Benedict,[4] found that males and females may have the condition in about equal proportions. In Benedict's group of cases the youngest patient was 5 weeks old, and in Friend's group the oldest patient was 80 years old. Flynn was inclined to believe that these cysts occur more commonly in the third decade.

We have tabulated 16 cases reported in recent literature in which more elaborate histories and detailed findings are obtainable. The various periods of time during which the complaints prevailed, with the number of cases in each instance, were as follows: 12 years, 1 case; 6 years, 1 case; 4 years, 1 case; 3 years, 1 case; 2 years, 4 cases; 1 year,

2 cases; 5 months, 1 case; 4 months, 1 case; 2 months, 2 cases; 3 days, 1 case, and 8 hours, 1 case.

SYMPTOMATOLOGY

From the foregoing figures it will be seen that in 14 of the 16 cases there have been from two months to twelve years during which the patients have been more or less ill, complaining and affording an opportunity for diagnosis. Some of these complaints include malaise, loss of strength, loss of weight, easy fatigability, feeling of nausea, occasional vomiting, abdominal pain to varying degrees from a dull ache to spells of greater severity, and a palpable tumor in half of the cases. Two patients had abdominal distention for one year, and another patient for six months. There was abdominal tenderness in 12 cases. This was usually generalized over the abdomen but often localized at the umbilicus, to the right or in the lower portion of the abdomen. Rigidity occurred in the acute cases. The white cell count, which was stated in 9 cases, was above 10,000 in 8 cases and was over 20,000 in 4 cases.

DIAGNOSIS

Flynn and Swartley made the observation that a correct diagnosis had not been made before operation or autopsy. This observation is borne out in the recent group of 16 cases that we have tabulated. A mesenteric tumor was, however, suggested in the diagnosis on two occasions. There is no grouping of symptoms characteristic of this disease. The acute cases usually suggest intestinal obstruction or peritonitis. Rupture of a cyst and immediate pain, nausea and vomiting in a woman would suggest ruptured tubal pregnancy. The long-standing cases have no characteristic diagnostic features. The abdominal tumor, if single, is smooth and rounded, and fluctuation can usually be made out. It does not move with respiration. The tumor, if multilocular, as in our case 1, may have an irregular or nodular feel. A tumor in the mesentery should be freely movable, often excessively so, both in vertical and horizontal directions, and moving it may cause pain. The point of attachment may be approximately located, usually quite centrally in the abdomen. The patient may find relief by turning and lying in certain positions, as on the side, with extreme flexion of the hip and knee joints, a point mentioned by Freudenthal.[5] A long-standing history, not paralleled by wasting, may rule out a malignant growth. As chylous ascites has been encountered with more or less frequency at operation, it would seem that diagnostic puncture or tapping would lead to valuable information. The enema of barium sulphate is of value in ruling out involvement of the colon. Screening

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5. Freudenthal, P.: Chylous Cyst of the Mesentery, Hospitalstid. **71**:353 (April 12) 1928.

of the stomach, used by Joyce and co-workers,[6] may show a pressure defect. Pneumoperitoneum with screening or with the roentgenogram has been suggested by Flynn as offering possibilities in the determination of the presence and location of the cyst. Differentiation must be made from fluctuant masses in the omentum, from the pancreas, and from ovarian cysts, retroperitoneal tumors and lipoma.

ETIOLOGY

Klemm found the wall of a true cyst to arise from mesoderm, and he believed, therefore, that such cysts are of embryonic origin. Kauff-
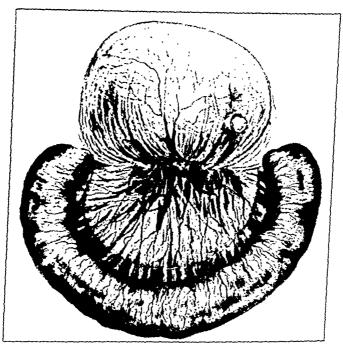

Fig. 4.—Cyst separated from the mesentery and turned back showing a nodule in the wall of the cyst. (From Friend.)

mann divided the mesenteric tumors into primary and secondary. The primary ones originated from the peritoneum itself—the endothelial type. Those behind the peritoneum he regarded as more common. If they were cystic and located between the layers of the mesentery, he regarded them as lymphangiomatous or as lymphangiocavernous tumors. The cystic mesenteric tumors may contain chyle, in which case they are called chylangiomas. They may be single or multilocular. Most of them are found in the mesentery of the small intestine, usually in the mesentery of the ileum. Cystic degeneration of the lymph gland is especially mentioned as the causative factor in the

6. Joyce, T. M.; Howard, M. A., and Fitzgibbon, J. H.: Chylous Cyst of the Mesentery, Northwest Med. **29**:123 (March) 1930.

origin of the cyst. It may be tuberculous as a result of tuberculous ulcers of the intestine, or it may result from a temporary blocking of the gland and degeneration following enteritis or some other inflammatory process, as appendicitis. Friend showed, in illustration of his article, the wall of a cyst in which a nodule at the side and intimately a part of the wall seems to be the original gland from which the cyst developed (fig. 4). In our case 2 the largest gland at the base of the mesentery contained in its cavity many leukocytic cells, lymphatic cells, a fibrinous network and very numerous, often intracellular, fat droplets of varying sizes. In Freudenthal's case, the opinion, on microscopic examination, was that a cystic degeneration of the lymph gland was the causative factor.

TREATMENT

Surgical treatment offers the only hope of cure. Several different methods of attack have been used. Porter, in his series of 20 cases, found that operation was performed in 14 and that in 6 the condition was discovered at autopsy. Of the 14 patients operated on, 3 died. Of those who had had an excision or enucleation of the cyst, 6 recovered and 2 died. When incision and suture of the sac to the abdominal wound was done, there were 5 recoveries. In 1 case in which excision of the cyst, mesentery and part of the bowel was done, death ensued. The mortality in the 16 cases of our tabulation, all methods of treatment included, was 25 per cent. Friend mentioned 25 cases in which incision and drainage were done with a mortality of 8 per cent and 18 cases in which extirpation was done with a mortality of 33.3 per cent. Begouin found that sewing of the sac to the abdominal wall, to be opened later, resulted in a mortality of 7.5 per cent. This was a better showing than that in a series of 60 cases in which extirpation was done. He collected reports of 54 cases in which puncture and aspiration were done without a fatality. Flynn, in 1912, resected the tumor and 40 inches (101.6 cm.) of bowel in a girl of 16 and obtained a recovery. Wilson[7] emptied the cyst found in a boy of 8 years, with recovery of the patient, but felt at the time of his report that the cyst was refilling. Alesen[2] excised the cyst in a girl of 5 and obtained a recovery. Benedict[4] stated that while all the patients on whom marsupialization was performed recovered, the deaths after extirpation or enucleation seemed to be due to primitive surgical methods, intestinal occlusion, peritonitis and other serious complications rather than to the method chosen. Modern surgical technic and preoperative preparation may serve in future cases to bear out this statement. The available methods therefore have been: (1) aspiration, (2) incision

7. Wilson, G. I.: Mesenteric Chylous Cysts, Brit. M. J. **1:**102 (Jan. 19) 1929.

and drainage, (3) enucleation and (4) marsupialization. Intestinal resection and extirpation will probably always carry a higher mortality. The choice of method should be made to fit the case.

SUMMARY

1. While mesenteric cysts were mentioned as far back as 1620, Rokitansky is credited with the first description of chyle cysts in 1842. Porter,[1] Friend,[2] Benedict[4] and Flynn have reported groups or reviews of cases, all of which have been considered in the present study. Chyle cysts of the mesentery are not common; indeed, they are relatively rare and have been encountered at all ages from early childhood to old age. In this paper a report of 2 cases has been added to the literature of the subject, and an attempt has been made to summarize the various symptoms that occurred in the reported cases. An effort has also been made to present the clinical features that may assist in leading to a diagnosis, a point which has been extremely baffling in the past.

2. From two months to twelve years elapsed in 14 of 16 cases during which time the patients were complaining and affording an opportunity for diagnosis.

3. Abdominal distention of greater or less degree was found in 10 of 16 cases.

4. A freely movable tumor in the lower part of the abdomen which fluctuates and has a midline attachment should suggest mesenteric cyst.

5. The discovery of chylous ascites by exploratory puncture may assist in establishing a differential diagnosis.

6. Marsupialization has resulted in the largest number of recoveries.

EXPERIMENTAL TRANSPLANTATION OF THE PANCREAS INTO THE STOMACH

A. M. TRIPODI, M.D.

Assistant in Surgery, St. Louis University School of Medicine; Assistant Surgeon, St. Mary's Group of Hospitals

AND

CHARLES F. SHERWIN, M.D.

Assistant Professor of Surgery, St. Louis University School of Medicine; Associate Surgeon to St. Mary's Group of Hospitals

ST. LOUIS

While the extensive investigative work on the pancreas proves that this gland is an essential organ in the human economy, the literature concerning surgical procedures on the pancreas is scanty and loosely scattered through medical journals and textbooks. The information that we gained from a search of the literature particularly impressed us with the fact that the present knowledge of diseases of the pancreas and the practical application of surgical treatment to the cure of these conditions are hardly any further advanced today than they were fifty years ago, when surgical treatment was limited to a few operations performed for the cure of retention cysts by excision or for the formation of an external fistula. Since that time a great deal of experimental work has been done in attempts to clear up the mysteries surrounding the function of the pancreas.

On the clinical side, Friederich (1878) summarized the meager knowledge of pancreatic disease that was available in his time. On the surgical side, it was not until the era of antiseptic and aseptic surgery and the consequent safe exploration of the abdomen that animal experimentation could be undertaken with hope of success and the pathology of the gland could be studied in the living human being.

Since Lister, physiology and surgery have developed hand in hand. Senn published his paper, "Surgery of the Pancreas," in 1885, and Fitz (1889) laid the foundation of the present knowledge of acute pancreatitis. Körte (1898), Oser (1898), Opie (1903), Robson (1907), Coffey (1909), Macleod, Banting and Best (1922) and de Takats (1930) are but a few of the prominent ones among an army of workers on

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the subject who approached the diagnosis and treatment of pancreatic disease from the basis of anatomy, pathology and physiology—the only proper and scientific basis.

In experimenting with the pancreas, because of its very nature—the unusual composite, complicated functions, the intimate relationship to other abdominal structures and the difficulty of surgical approach—one meets with many problems the importance of which is equaled only by their difficulty of solution. Every such difficulty encountered has impeded not only the clinician in his diagnosis and therapy, but also the surgeon in his technical mastery of the surgical problem.

In 1909, Coffey published a preliminary report entitled "Pancreato-Enterostomy and Pancreatectomy." His originality and the apparent delicacy of the technic he developed in completing his work were indeed a great inspiration to us; however, in performing his operation for pancreato-enterostomy, one of us met with little success. Coffey took a loop of bowel, the adjacent sides of which he sewed together. He then made an opening into the loop in the same way as Finney opens the duodenum and stomach in his operation for ulcer. Into this opening Coffey transplanted the pancreas. He stated that it made no difference which end of the sectioned pancreas was implanted, the current would flow normally or in reverse and discharge into the intestine.

Perhaps it was the technical difficulties of this operation that prevented its success. At any rate, we decided to perform similar experiments, using the stomach instead of the jejunum. At first we did not pay much attention to the study of the subject from the standpoint of physiology, our wish being to know whether in case of necessity this could be accomplished without bad effects on the animal. In this experiment we used seventy-two dogs. The object was to devise by direct surgical attack a rational method of treatment in certain cases of injury involving either the tail or the head of the pancreas, and of early tumor growth involving the head. In performing these operations, two essential points were constantly kept in mind: first, avoidance of leakage of the pancreatic fluid; second, the surgical disposal of the severed or injured end in such manner that both the internal and the external functions of the gland would be preserved.

We soon learned that the dog's pancreas is easily injured. The gland is better protected when not handled with any kind of instrument. The pancreas in the dog differs from the human pancreas in being covered with peritoneum. While this condition renders its implantation into the stomach a safer procedure, our first experiments failed because of leakage and peritonitis.

The surgical reasons for using the stomach instead of the jejunum were its accessibility, its favorably large size and the elimination of

any possible obstruction of the lumen of the bowel or strangulation of the gland, which might occur if it were implanted into the small intestine.

SERIES I

The first experiment consisted in making a pocket between the muscularis and the mucous coat on the posterior wall of the stomach (fig. 1). An inch and a half (3.77 cm.) of the distal end of the pancreas was removed entirely, and then the cut surface of the remainder was implanted into this pocket and held in place by a piece of silk tied around the end of the pancreas and fastened to the wall of the stomach at the bottom of the pocket (fig. 1 B). This kept the cut end of the pancreas anchored while two interrupted sutures were taken at the entrance on each side of the pocket in order to promote healing and to prevent leakage of the pancreatic fluid. Four weeks after the operation the dog was killed. A study
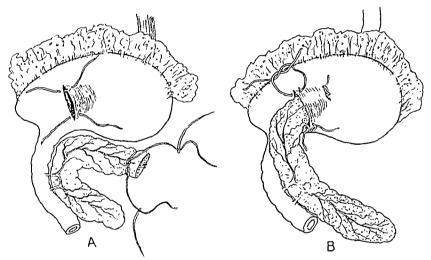
Fig. 1.—Implantation of the pancreas into a pocket in the wall of the stomach in series I: A, a pocket is made under the muscular coat in the posterior wall of the stomach. Sutures are placed in the stomach and pancreas. B, the cut end of the pancreas is sutured into the pocket in the stomach, preventing the discharge of pancreatic juice into the peritoneal cavity.

of the results of the operation revealed a firm, smooth union between the tail of the pancreas and the wall of the stomach. The pancreas was in a good state of preservation. There was no accumulation of pancreatic juice in the pocket nor any erosion (digestion) of the walls of the pocket.

A second experiment consisted in the removal of the tail of the pancreas for about 3 inches (7.6 cm.) ; the cut end of the pancreas was drawn into the stomach through a crucial incision, and the opening was closed around it (fig. 2). A study of the results of the operation (six to ten weeks later) revealed firm, smooth union between the pancreas and the wall of the stomach. The pancreas looked normal. Serial sections were taken about 25 microns apart throughout the entire area of contact of the pancreas with the stomach, and it was found that the mucosa of the stomach had completely grown over the defect produced at operation, and that there was a layer of connective tissue between the mucosa of the stomach and

the pancreatic tissue. The foregoing experiment was repeated in other dogs with this difference, that the main pancreatic duct was exposed and divided between ligatures. In these dogs, also, the mucosa was found to have united over the cut end of the pancreas. Presumably, the pancreas emptied itself into the duodenum by accessory ducts.
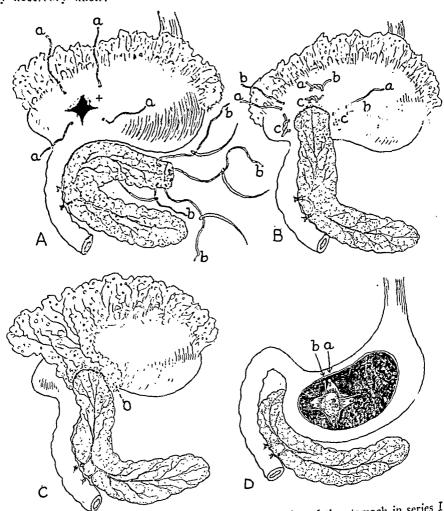

Fig. 2.—Implantation of the pancreas into the cavity of the stomach in series I: In *A*, *x* indicates the cross-incision in the posterior wall of the stomach; *a*, the flap-inverting sutures; *b*, the pancreas traction and anchoring sutures. In *B*, the pancreas is drawn into the stomach and its traction sutures (*b*) tied to the flap-inverting sutures (*a*); additional sutures of the stomach to the pancreas (*c*) are placed as in series II and III. In *C*, omentum (*o*) is sutured around the anastomosis as in series II and III. *D* shows the interior view of the anchored stump of the pancreas and the inverted stomach flaps, as in series II and III.

SERIES II

In this series we removed the head of the pancreas and implanted the remaining end into the cavity of the stomach (fig. 3). It must be stated here that in the dog the main pancreatic duct enters the duodenum from near the middle of the

pancreas. This duct was divided between two ligatures, but no attempt was made to sever all of the possible accessory ducts.

A study of the results of the operation again revealed good union between the wall of the stomach and the pancreas but no communication between the pancreas and the lumen of the stomach, probably for the same physiologic reason as in series I. The pancreas looked normal except for patchy foci of inflammation about the old sutures (figs. 7 and 8).
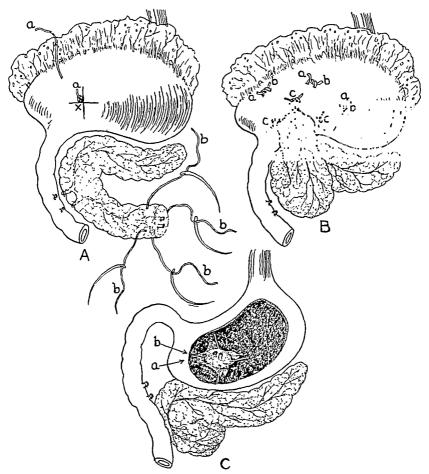
Fig. 3.—Implantation of the pancreas into the cavity of the stomach in series II. The explanation is the same as for figure 2, except that the head of the pancreas was removed and the stump was implanted into the cavity of the stomach.

SERIES III

In these experiments the head and neck of the pancreas were removed. The stump was dissected 1 inch (2.5 cm.) beyond the point where the pancreatic ducts enter the duodenum (fig. 4). Here an attempt was made to cut through all duct connections to the duodenum. The central duct was exposed from ½ to 1 inch and bleeding controlled. Clear pancreatic fluid could be plainly seen escaping

from the duct. The stump was then implanted into the posterior wall of the stomach as follows:

A triradiate or crucial incision, large enough to admit the end of the pancreas freely, was made into the posterior wall of the stomach about 1 inch above the great curvature and near to the pylorus, thus forming three or four flaps (fig. 4 *A*, *x*). A silk suture was passed through the point of each flap and tied. This was used to invert the flap by passing the suture into the cavity of the stomach and out through the wall 1 inch away from the cut edge. By pulling on
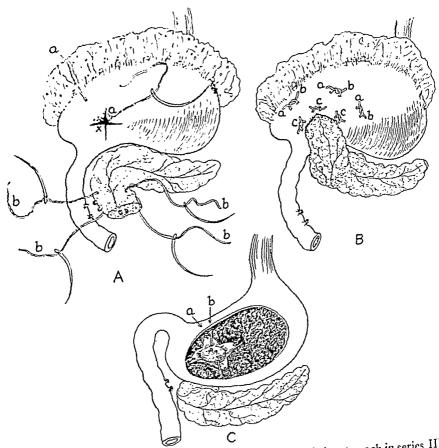

Fig. 4.—Implantation of the pancreas into the cavity of the stomach in series III. The explanation is the same as for figure 3, except that the head and neck portion of the pancreas was excised, and the stump with its duct orifices patent was implanted into the cavity of the stomach.

these sutures the ends of the flaps were inverted, a smooth peritoneal entrance for the stump of the pancreas being formed. One silk suture was passed through each side of the pancreas about 1 inch from the end to be implanted (fig. 4 *A, b*). These sutures were used as traction sutures to draw the stump of the pancreas into the lumen of the stomach. These were now carried through the aperture into the stomach and out again through the posterior wall a little distance from the exits of the flap-inverting sutures. These were then tied one to each of the flap-inverting sutures, thus anchoring the inverted ends of the flaps and preventing retraction of the pancreas (fig. 4 *B* and *C, a-b*). An additional row of sutures

was taken, the stomach being sewed to the pancreas (fig. 4 B, c). A small piece of omentum was drawn around the implanted pancreas and secured to the stomach wound by one or two sutures (fig. 2, C, o).

The abdomen was closed with catgut, without drainage, and the skin sutured with catgut and treated with iodine. Some of our dogs had been anesthetized with ethyl carbamate hypodermically. These died within forty-eight hours. In all we found serious hemorrhage into the stomach. We also lost several dogs from pneumonia. In no case was there any apparent leakage of gastric juice or any infection.

Of the surviving dogs, three were allowed to live for about nine months, during which time they were kept with a control dog. They fed on dog biscuits for about four months, then large amounts of meats and fats, then excess carbo-
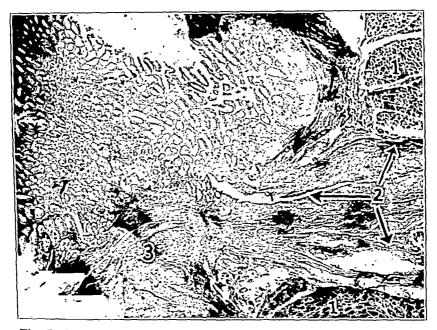
Fig. 5.—Photomicrograph showing normal pancreatic tissue (*1*), a pancreatic duct with its lumen (*2*) and the firm fibrous union to the muscularis of the wall of the stomach (*3*).

hydrates, and later on mixed refuse from the cafeteria. All the dogs lost weight on the dog biscuit diet but gained on a mixed diet.

Gastric contents, blood and urine were obtained at five week intervals.

Gastric analysis revealed that the pancreatic lipase (copper soap method) was strongly positive in all three dogs, except at one examination of one dog, and never in the control dog.

Trypsin was found in the stomachs of two dogs; questionable or negative reactions to the test were given by one dog, and trypsin was never found in the control dog.

Blood sugar varied from 50 to 105 mg. per hundred cubic centimeters in the dogs on which operation was performed, and from 66 to 83 mg. in the control dog. After four weeks on a diet high in carbohydrate, the blood sugar was 67, 71 and 71 mg. in the dogs on which operation was performed and 77 mg. in the control dog.
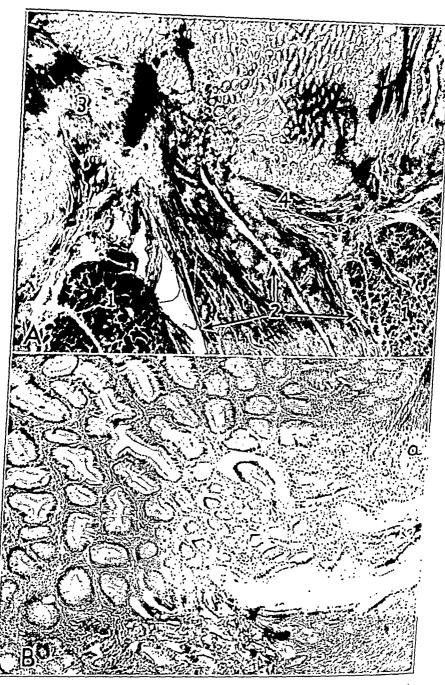
Fig. 6.—*A*, photomicrograph showing normal pancreatic tissue (*1*), a large pancreatic duct with its lumen (*2*), the firm fibrous union to the muscularis of the wall of the stomach (*3*) and muscularis mucosae (*4*). *B*, high power photomicrograph showing normal pylorus mucosae and glands, with continuity of the muscularis mucosae with the walls of the duct (*a*).

Fig. 7.—Fresh specimen from a dog six weeks after severance of the head of the pancreas and transplantation of the stump into the cavity of the stomach: 1, spleen; 2, posterior wall of the stomach; 3, pancreas firmly united with the wall of the stomach.

Fig. 8.—A, fresh specimen from a dog ten months after transplantation of the stump of the pancreas following excision of the head and neck: 1, spleen; 2, posterior wall of the stomach; 3, pancreas healed to the wall of the stomach. B, inside view of the stomach showing the point where the pancreatic duct communicates with the cavity of the stomach.

Urine obtained by catheter never showed sugar in either the operated dogs or the control dog.

These dogs were killed after from nine to ten months. One dog which remained undernourished, at autopsy, after nine months, showed a gross complete atrophy of the pancreas, possibly due to the damage to its blood supply or to its ducts, but did have an enormous hypertrophy of the gastro-intestinal tract. This is undergoing further investigation. Microscopic examination of the site of implantation in the other dogs showed that the gross pancreatic tissue within the stomach was digested, but the duct was in continuity with the lumen of the stomach (fig. 5).

These two specimens in which the cephalic end of the pancreas was united to the stomach were cut in serial sections. In both specimens the pancreatic tissue attached to the wall of the stomach was normal, and a large duct was discovered just under the gastric mucosa (fig. 6). In one specimen the duct connection to the surface could not be definitely followed, although there were indications of a small duct system continuous with the gastric mucosa. The second specimen demonstrated a large pancreatic duct in which the lumen was continuous with that of the stomach, and continuity of the mucous membrane of the stomach with that of the duct was easily demonstrable (fig. 6). There was no evidence of any pathologic reaction within the wall of the stomach or the mucosa. The failure of the duct to heal in and establish continuity with the mucosa of the stomach in the first series, we attributed to the presence of an accessory duct or ducts, but it must be stated that in the first series the opening into the stomach was farther away from the pylorus than it was in the second series. The experimental evidence suggests that implantation should occur into the pyloric end rather than into the fundic end of the stomach. The free anastomosis about the pancreas seems to take care of the blood supply of pancreatic tissue no matter which part is implanted, and this is borne out by the excellent preservation of the pancreatic substance, both in gross and in microscopic specimens (figs. 5, 6, 7 and 8).

CONCLUSION

The pancreas may be successfully implanted in the stomach, and its internal and external functions preserved.

The establishment of the possibility of surgical connection between the pancreas and the stomach opens an extensive program of research for both surgical and physiologic investigators.

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CRANIAL OSTEOMAS AND HYPEROSTOSES PRODUCED BY MENINGEAL FIBROBLASTOMAS

A CLINICAL PATHOLOGIC STUDY

FRANCIS ECHLIN, M.D.
NEW YORK

Clinically, an osteoma of the cranial surface may sometimes closely simulate a hyperostosis produced by a meningeal fibroblastoma (dural endothelioma, meningioma). The importance of distinguishing between these two lesions, so different in their ultimate results, lends intrigue to an already interesting study.

In the recent literature considerable attention has been given to hyperostoses resulting from infiltration of the skull by meningeal fibroblastomas. From a clinical and operative point of view, this attention has also been extended to osteomas about the frontal sinus [1] and orbit.[1a] A study of osteomas of the external surface of the cranium, however, would appear to have been largely neglected. Judging from the material in this laboratory, the latter osteomas occur almost as frequently as clinically recognizable hyperostoses cranii produced by meningeal tumors.

An attempt shall be made in this paper to explain the true nature of osteomas of the external surface of the cranium as well as their clinical, pathologic and roentgenographic differentiation from hyperostoses produced by meningeal fibroblastomas.

The material for this article was collected in the Surgical Pathological Laboratory of the Johns Hopkins Hospital from approximately 2,000 cases of tumors of the bone and 1,000 cases listed under tumors of the head and skull, which included approximately 350 cases of tumor of the brain. All the osteomas of the external surface of the cranium or hyperostoses caused by meningeal fibroblastomas were verified by microscopic examination.

OSTEOMAS OF THE EXTERNAL SURFACE OF THE CRANIUM

Under this heading are included osteomas which apparently arise from preosseous tissue on the cranial surface. If one attributes osteo-

genic powers to the periosteum, then these osteomas may be regarded as apparently arising in the deeper layers of this tissue. On the other hand, if one is of the belief that the periosteum includes only the outer layer of fibrous tissue covering the skull, which seems to act as a limiting membrane only, then these osteomas must be regarded as apparently originating in the underlying preosseous tissue.

Whether the cranial osteomas should be classed as true neoplasms is a debatable question. Ewing[1b] wrote:

> Circumscribed overgrowth of bone occurs under such a wide variety of conditions and the distinction between inflammatory and neoplastic hyperplasia of the tissue is so often obscure that it has never been possible to define the limits of osteomata. In discussions of osteomata, it is customary to include all forms of overgrowth of bone, thus securing an effective comparison of true and partial bony neoplasms.

Not quite such a broad classification is adhered to in this article, as there are a number of osteomas arising from the external surface of the cranium, which appear to comprise a distinct group with special characteristics, that are worthy of individual consideration. In order to define the boundaries of this special group, it is well to exclude those apparently similar cranial osteomas arising from the frontal sinuses, orbit and inner table of the skull, the ventral symmetrical hyperostoses of the inner table of the calvarium and also certain other lesions with known etiology, often referred to as osteomas, such as hyperostoses produced by osteomyelitis, syphilis and similar conditions, and finally, osteochondromas. The groups not included in the main class of cranial osteomas to be presented deserve brief mention.

Osteomas of the frontal sinus and orbit are not well represented by the material from this laboratory. Their origin and mode of development are still the subject of debate. Many of them appear to arise from the deeper layers of the periosteum or subperiosteal preosseous tissue and present in their growth both spongy and eburnated forms. They apparently are the result of a process similar to that special group of osteomas to be described. They arise in a different situation and, unlike osteomas of the cranial surface, cause early damage to vital structures. They sometimes cause a swelling of the outer table of the skull by pressure, but by roentgenographic study are easily distinguishable from osteomas arising on the cranial surface.

Osteomas of the inner table, which have also been excluded from detailed description, seem to represent a similar process, but appear to arise from the endocranium on the intracranial surface of the skull. Three osteomas of this type were found in the laboratory. None of them showed a demonstrable change in the outer table of the skull.

1b. Ewing, James: A Text Book of Neoplastic Disease, Philadelphia, W. B. Saunders Company, 1928.

In their symptomatology they were indistinguishable from meningeal fibroblastomas.

Symmetrical hyperostoses of the inner table of the calvarium usually are found only at autopsy, occur most frequently in females and are confined particularly to the frontal region. They are usually symptomless. Yolton's [2] paper should be consulted for a more detailed description.

The other cases found in the laboratory which should be excluded before a presentation of the more special group of osteomas is attempted are as follows: One was the case of a man, aged 34, who presented exostoses of the frontal, malar and clavicular bones and a positive Wassermann reaction; the growths disappeared rapidly following antisyphilitic treatment. In the next case there was a microscopically unverified osteoma of the external auditory canal, apparently similar to that reported by Lillie and Williams. [3] The last case was that of a patient, aged 15, presenting an osteochondroma of the occipital bone at the site of attachment of the trapezius muscle (fig. 1). The fact that in the roentgenogram this tumor showed a cartilaginous cap and arose from the basi-occipital bone, which is preformed in cartilage, at the site of attachment of the trapezius muscle in the tendon of which precartilaginous connective tissue may be found, excludes this case from the main series to be described.

When the foregoing cases are excluded, there is left a group that presents special characteristics. This group is the one presented here.

The special group of osteomas discussed in this paper are benign bony tumors usually arising before or about puberty from the external surface of the cranium and most frequently involving the frontal bone. The symptoms, as a rule, are mild, but rarely definite signs of compression of the brain or of cortical irritation may arise late in the course of the disease. In this series the average duration of the tumor at the time of operation was nineteen years, but a case is recorded with a history of only one year's duration and another of sixty-six years. The roentgenographic picture varies according to the stage of development of the tumor. Thus, it may show a small button-like tumor on the surface of the outer table, an enormous subperiosteal bony tumor with complete absorption of the outer table and involvement of the diploe in places, or, finally, a spongy or eburnated osteoma lying with its base on the inner table and showing on its surface a bony shell. Microscopically, the tumors are either eburnated and composed of quiescent adult corti-

2. Yolton, L. W.: Ventral Symmetric Hyperostosis of Inner Table of Calvarium, Tr. Chicago Path. Soc. 13:181 (June) 1930; Arch. Path. 9:534 (Feb.) 1930.

3. Lillie, H. I., and Williams, H. L.: S. Clin. North America 11:801 (Aug.) 1931.

cal and cancellous bone, or spongy with proliferating preosseous tissue and young trabeculae of cancellous bone. Between these two types are found osteomas showing intermediary stages of ossification. On the surface of apparently all types of osteomas is a layer of fibrous tissue (periosteum), which in the spongy type and in certain small areas in the eburnated type shows in its deeper layers a gradual transition through a fibrospindle cell stage to an adult preosseous tissue, actively concerned in bone formation. Later it is pointed out that the eburnated and spongy osteomas are only different stages of the same process, and that they apparently all arise from the deeper layers of the periosteum or subperiosteal preosseous tissue which lies on their surface.

Fig. 1 (path. no. 47270).—Roentgenogram showing an osteochondroma arising from the occipital bone near the attachment of the trapezius muscle, the tendon of which contains precartilaginous connective tissue. Note the cartilaginous cap and the tendency of the tumor to develop in a longitudinal manner, outwardly from the bone.

PRESENTATION OF CASE HISTORIES

CLINICAL FEATURES

The present analysis is compiled from nineteen cases of osteoma of the outer surface of the cranium reported in the literature and seven cases found in the Surgical Pathological Laboratory of the Johns Hopkins Hospital.

All of the patients complained of a bony hard tumor or osteoma of long duration attached to the surface of the skull.

Etiology.—In five cases, the sex was not recorded, but in the others, twelve of the patients were females and nine males. There was a history of trauma prior to the appearance of the tumor in eight cases, but the majority seem to have arisen spontaneously. A low grade periostitis may have played a rôle in the production of some of the growths and particularly in those in which the skin was broken at the site of trauma and in those arising near the frontal sinuses or mastoid portion of the temporal bone, but there is no definite proof of this. No history of rickets was noted in this series.

In no case was there any suggestion of a hereditary factor influencing the growth of the osteoma, although in two cases the tumor was present at birth. Trauma at birth must be considered as a possible factor.

It is interesting to note that in fifteen cases the patient was 12 years of age or younger when the growth first appeared, and in ten cases the osteoma was noted before the patient was 8 years old. No age of onset is given in five cases, but the eldest of these patients was 31 years old and when one considers the slow growth of the usual osteoma, it is logical to believe that these five patients also were young at the onset of the tumor. The other six patients ranged from 14 to 31 years of age when the tumor appeared.

Signs and Symptoms.—A bony, hard, nonmovable, painless lump protruding from the surface of the skull was the first sign noticed in all patients.

In the twenty-six cases, thirteen osteomas were almost totally restricted to the frontal bone. Five tumors involved particularly the parietal bones, but three of these also involved the frontal bone. The remaining eight tumors were attached to the temporal bone, but several of these encroached on the parietal bone and two on the occipital.

The majority of the osteomas grew slowly and steadily, but in some cases trauma to the tumor or incomplete removal at operation precipitated an acceleration in growth. In case 23, the tumor appeared spontaneously to grow more rapidly about puberty.

The great majority of histories indicate that the condition was symptomless, but in the histories of more recent years and particularly in my own cases, dizziness, headaches, a sense of pressure and pain about the lump were noted. From only three patients was there obtained a history of symptoms of cerebral damage, one of these having had epileptic seizures fifty-three years after the onset of the tumor, another increasing symptoms of a right-sided cerebral lesion following a serious fracture of the skull in infancy, and the third patient (case 5), mental retardation. Fainting spells were noted in case 7, but these may have been functional.

The duration of the tumor at the time of operation is recorded in nineteen cases, and in fourteen of these there was a history of over eleven years, the average time being twenty-four years. The histories in the other five cases dated back from one to ten years. The average duration of the tumor, taking the nineteen cases collectively, was nineteen years.

The rarity of severe symptoms and the protracted course of these lesions indicated their benignancy. Von Eiselberg[4] and Bassoe[5] each reported a case with secondary malignant change in an atypical cranial osteoma. Bassoe's case was that of the famous giant, Wilkins. Secondary sarcomatous change in exostoses (osteochondromas) elsewhere in the body is comparatively common, but these tumors, as is well known, are chondromyxosarcomas, having their origin in precartilaginous connective tissue which is apparently absent about the cranial vault. Geschickter[6] collected eighty of these cases.

Physical Examination.—As far as can be ascertained, the majority of the patients appeared healthy and intelligent, but there was some mental retardation in case 5. In only one instance (case 5) is there a record of fever or increase in the pulse rate, and in this case the cause of the fever was uncertain.

The osteomas varied in size from that of a small walnut to that of a grape-fruit, but the original tumor in some cases was as small as a pinhead. The skin over the growth was freely movable and appeared normal except in case 7, in which an increase in vascularity was noted, and in a few cases in which a scar of a previous operation was present. The majority of the osteomas were in the frontal region and four of them at least involved the glabella of this bone. In every case the tumor was bony, hard, nonmovable and firmly attached to the skull. In most cases, it was smooth, rounded, broad-based and semispherical, and appeared to shade imperceptibly into the surrounding skull. In some cases, the surface was slightly irregular and somewhat lobulated. Small button-like osteomas lying on the external table of the skull have been mentioned by Virchow,[7] and a picture of a similar osteoma on the surface of the frontal bone is shown by MacCallum[8] "separated from

4. von Eiselberg, F.: Zur Casuistik der Knocheren Tumoren des Schadeldaches, Arch. f. klin. Chir. **81**:1, 1906.

5. Bassoe, P.: Concerning an Exostosis of the Skull Undergoing Sarcomatous Change, J. Nerv. & Ment. Dis. **30**:513, 1903.

6. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1931.

7. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald. 1863, vol. 2, p. 1.

8. MacCallum, W. G.: A Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1928.

the skull around the edges so as to appear pedunculated." Similar small osteomas have been found attached to the surface of the facial bones.

Two osteomas were present on the skull in four of the cases, and tenderness over the growth was present in two. Osteomas were found elsewhere on the skeleton in two cases, and there was also a case in which there were symptoms of a right-sided cerebral lesion with signs of left hemiplegia, internal strabismus and a history of fractured skull. Percussion over the osteomas gave results similar to that done elsewhere over the cranium, and no cracked-pot sound was noted. Auscultation when done likewise gave negative results.

General physical and neurologic examinations gave apparently negative results, except as already stated. The white blood cell count was slightly elevated in two cases. This may have been due to poor counting, as the hemoglobin, temperature and pulse rate were normal in these cases. No other abnormalities in morphologic or serologic blood studies were recorded, nor was there anything of importance noted in the urine of these patients.

ROENTGENOGRAPHIC FEATURES

The literature unfortunately contains little of value concerning the roentgenographic features of the osteomas of the cranial surface. Only seven good roentgenograms were found, two of these in the literature (cases of Marey[9] and Orator[10]) and five in this laboratory. All the tumors, six of which were of the spongy type and one of the eburnated type, had been present for over twelve years when the roentgenograms were taken.

Although the number of roentgenograms available limit the scope of the study, there are many features characteristic of osteomas which give valuable clues to their origin, mode of growth and early appearance, as well as aid in differentiating them from other cranial lesions.

The seven roentgenograms show a smooth or slightly irregular and in some cases faintly lobular domelike swelling, extending outward for a varying distance from the surface of the skull. The base of the mound in every case is formed by the inner table of the skull which appears thickened and in most cases slightly depressed.

In six cases the body of the tumor is continuous with the diploe, the outer table of the skull having completely disappeared. In the rotengenograms for cases 1, 4, 5 and 6, a thin layer of bone extends over the surface of the dome of the tumor, being most pronounced in

9. Marey, Georges: Contribution à l'étude d'une variété particulière d'exostose de la voûte crânienne, le spongiostéome, Thèse de Paris, 1910, no. 87.

10. Orator, V.: Beitrag zur Chirurgie der Schadeldachosteome, Deutsches Ztschr. f. Chir. **233**:459, 1931.

case 1 in which the growth is an eburnated osteoma. These roentgenograms give one the impression that the tumor arose in the diploe and pushed the outer table before it in its growth. This is what appears to have taken place and is the accepted theory, but it seems unlikely that a new growth arising in the diploe could produce an original tumor the size of a pea, which was true in case 5 (fig. 2), without first passing through the outer table. If the growth did pass through the outer table, then the theory of its expansion before the tumor is incorrect. If the tumor arose in the diploe, the swelling would in all probability have been more fusiform with more depression of the inner table than is seen. Microscopically, it is shown below that the shell of bone over the surface of these neoplasms is new bone in the process of being formed from preosseous tissue and is not the expanded outer table.

Fig. 2 (case 5).—Roentgenogram of an enormous spongy osteoma which arose from preosseous tissue on the surface of the frontal bone. The tumor is continuous with the diploe. A thin shell of new bone lies on its surface, and its base is formed by a thickened and slightly depressed inner table of the skull. The inner table, although wavy in outline, is smooth and clearly demarcated. The frontal sinuses are enormous, but there is no tendency for the tumor to fill them.

The density of the body of the osteomas varies from about that of the diploe to a very dense shadow, as is seen in the eburnated tumor. The dome of the tumor in Orator's [10] case presented an irregular mottled appearance of increased density, characteristic of the irregular laying down of more adult bone. An anteroposterior view of some spongy osteomas shows what appears to be an erosion of the skull. The spongy nature of the bone is usually responsible for this appearance of erosion.

The frontal sinuses are enlarged, although empty, in those cases in which the tumor encroaches on the glabella of the frontal bone. In one case they are enormous (fig. 2).

The roentgenogram (fig. 4) in case 7 presents a picture of considerable importance, as it gives some indication of the origin and subsequent

mode of growth of these tumors. It shows particularly the lateral edge of the tumor where there is evidence of a largely absorbed, moth-eaten looking, but still partially persistent, outer table of the skull, passing through the depth of the tumor with the greater portion of the tumor overlying this outer table. At the extreme periphery of the osteoma where the outer table is best preserved, there is considerable bony sub-periosteal proliferation. The diploic space throughout appears little wider than normal. A roentgenogram of a cross-section taken through the center of the tumor, however, shows no evidence of the old outer table; it apparently had undergone complete spongy transformation or absorption (fig. 5). Roentgenographically, the tumor as a whole presents a fluffy mottled appearance with areas of increased porosity and new bone formation with a tendency for the bone spicules to be laid down in a somewhat peripherally radiating fashion on its surface.

Fig. 3 (case 6).—Roentgenogram showing a spongy osteoma involving the frontal bone. The tumor shows a very thin shell of new bone on its surface. It is continuous with the diploe. Its base is formed by a thickened and slightly depressed inner table of the cranium. The inner surface of the skull underlying the osteoma is smooth. The left frontal sinus is enlarged. This tumor was eburnated at its lower periphery.

This picture in a long bone would suggest a malignant growth. This malignant appearance is frequently seen in benign growths arising in membranous bone. The base of the tumor in its middle portion, as pointed out, is formed by a somewhat thickened and slightly depressed inner table.

From figure 5 it appears that the osteoma did not arise in the diploe, but in the periosteal region where the formation of considerable new bone of a porous appearance occurred, and finally most of the outer table became absorbed or likewise transformed into spongy bone. This spongy transformation of the outer table is seen particularly in the cross-section through the center of the tumor. The tumor, therefore, in time having completely absorbed the outer table of the skull, would be everywhere continuous with the diploic space and appear to be arising

from it. If these observations are correct, this osteoma represents an earlier stage in development than the six osteomas previously described, in which the old outer table had completely disappeared in the regions of the osteoma, and in some cases a layer of bone had been laid down on the surface of the tumor. Carrying the idea further, one may imagine

Fig. 4 (case 7).—Roentgenogram showing the periphery of a spongy osteoma. Subperiosteal bony proliferation overlying a partially intact outer table of the skull is evident, especially at the right hand edge of the osteoma. The plate shows evidence of some radial arrangement of the new bone. This picture could be easily confused with one of an exostosis overlying a meningeal fibroblastoma. Figure 5, taken to show the central regions of the tumor, easily differentiates it from a hyperostosis of meningeal origin. Note that the inner table is slightly depressed, but clearly outlined.

Fig. 5 (case 7).—Roentgenogram of a cross-section through the center of the tumor shown in figure 4. The dome-shaped nature of the spongy osteoma is well shown here. The outer table of the skull has undergone a spongy transformation or absorption and is no longer evident. The bone is arranged in a radiating fashion only near the surface of the tumor. The inner table shows the markings of the meningeal vessels, and, unlike the exostoses produced by meningeal tumors, shows no evidence of new bone formation extending downward from its inner surface. The roentgenogram was taken at an angle which accounts for the appearance of roughening on the inner surface of the skull.

that the osteoma in case 7 was originally a small spongy growth arising on the surface of the outer table. In support of this idea, it should be

mentioned that I have found a number of small, spongy osteomas in the periosteal region about the membranous bone of the face.

GROSS PATHOLOGY

A correlation of the observations recorded at operation with those made on examination of the gross specimens proves of value in the determination of the nature of these cranial osteomas. Although many of these tumors present a difference in gross structure, the origin and mode of growth appear to be essentially the same in all types. These differences in gross structure seem to represent only separate stages in the development of osteomas. The nature of the tumor appears to be influenced in part by the age of the patient.

In the gross some of the tumors lie flat on the surface of the skull, apparently being attached only to the outer table. Others appear to penetrate as far as the outer layers of the diploe, and there are finally tumors which lie with their base on a thickened and slightly depressed inner table, the outer table having completely disappeared.

The consistence of these osteomas likewise varies, some being spongy and cancellous (spongy osteomas), others eburnated or hard (eburnated osteomas).

Even among the spongy type differences in structure can be detected, but apparently all of them show dense fibrous tissue on their surface, which fuses with the surrounding periosteum. This fibrous tissue is often abundant. Some of the tumors show a layer of bone beneath this fibrous tissue, while in others it is absent. This layer of bone may be continuous, thick and hard, or irregularly distributed, thin and easily broken through. When it is present, it is usually continuous with the outer table of the skull, and beneath it there is relatively avascular, tough, cancellous bone continuous with the diploe. In those cases in which no layer of bone is present, the fibrous tissue on the surface becomes directly continuous with an underlying soft, vascular, more mushy cancellous bone than that above, which usually can be followed inwardly to the inner table of the skull and is everywhere in direct continuation with the diploe. The larger osteomas arise, as a rule, before puberty and are usually of the spongy type that show cancellous bone extending to the inner table.

The so-called eburnated osteomas present a more uniform picture. The same type of fibrous tissue lies on their surface, but cortical bone is present beneath this tissue in all cases. Extending toward the depth of the tumor from the undersurface of the cortical bone, there is usually adult cancellous bone which is hard and much more difficult to cut than that encountered in the spongy osteomas. Cortical bone may, however, predominate throughout the whole tumor. The eburnated tumors are, as a rule, small and may lie with their base on the inner table or, per-

haps, as in the cases mentioned by Virchow [7] and MacCallum,[8] may lie flat on the surface of the skull like a button, being attached only in their more central regions. This type of tumor is more common about the facial bones. Of the five patients in this series who were over 21 years of age at the onset of the tumor, four presented osteomas of the eburnated type, and in case 1, although the nature of the original tumor is not known, the recurrent one arising when the patient was 22 years of age was of the eburnated type. A tendency of the osteomas arising in adults to be eburnated is therefore evident.

It should be mentioned that in case 3 two small perforations of the skull were present at the edge of the osteoma. Infection may have been a factor in this case.

MICROSCOPIC FEATURES

The microscopic picture of an osteoma of the outer table of the cranium varies according to the stage of development of the tumor and the age of the patient. On the surface of apparently all of the osteomas, there is a layer of fibrous tissue (periosteum) under which may or may not be a layer of cortical bone. The center of the tumor is usually made up of cancellous bone, either of the young or of the adult type.

The microscopic picture of an eburnated osteoma shows on the surface of the tumor a comparatively thick layer of hyalinized looking, relatively anuclear fibrous tissue (fig. 6), which in some sections shows small areas of underlying preosseous tissue which is engaged in the formation of new bone (fig. 7). This fibrous tissue is firmly adherent to underlying cortical bone and in many places dips into it, forming a homogeneous union with the bone. The underlying cortical bone is of the adult type with well defined, concentrically arranged lamellae and small haversian canals, and is relatively avascular. This bone usually shows a gradual transformation to a more cancellous type as the center of the tumor is approached, and in this region is seen an interlacing of adult laminated bony spicules, with relatively wide intertrabecular spaces containing scanty but normal looking hematopoietic elements. In some of the osteomas, cortical bone predomintes throughout (fig. 6). These eburnated osteomas may present a layer of cortical bone on their inner as well as on their outer surface, which is the old, inner table of the skull (fig. 8). In some of these tumors no formation of new bone is seen except subperiosteally (fig. 7).

The microscopic sections of the spongy osteomas do not show such a quiescent picture. On the surface of the tumor is seen a hyalinized-like fibrous tissue, poor in nuclear material and identical in appearance to that described previously (periosteum). But in the deeper layers of this connective tissue, there is a gradual transition from an elongated spindle cell stage to a more mature definite preosseous tis-

sue containing young osteoblasts (figs. 9 and 10). The osteoblasts are lined in rows along irregularly scattered trabeculae of young bone in the formation of which they are actively participating. Over a small area toward the surface of the tumor in some sections, there is a tendency for the new bone to be laid down in a peripherally radiating fashion (fig. 9), but elsewhere throughout the tumor the trabeculae are everywhere arranged in an irregular manner. This irregular distribution of trabeculae is well shown in the roentgenogram. In some of the sections of this type, the spongy bone extends from the surface of the
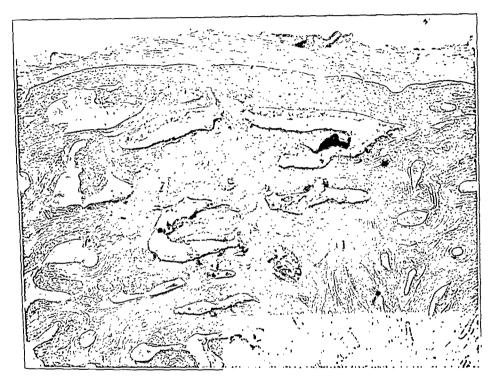
Fig. 6 (case 1).—A low power photomicrograph of an eburnated osteoma showing abundant quiescent, relatively anuclear fibrous tissue (periosteum) on its surface.

tumor to the inner table of the skull, the inner layers of which are sometimes transformed into spongy bone of a more dense nature than that seen in the center of the tumor (fig. 11). This type of spongy bone extends over a wider area than the normal inner table and hence could account for the thickening seen in the roentgenograms. In no section is there evidence of new bone formation on the part of the endocranium (endosteum), and if this does take place in some cases, it must be small in amount or severe symptoms of compression of the brain would ensue, which rarely happens in this type of osteoma.

On the contrary, the endocranium appears to act in some measure as an internal limiting membrane preventing any marked depression of the inner table. It is possible in some cases that the inner table may become completely transformed into spongy bone, and although this has never been observed, it would account for the slight depression of the inner table which is so frequently seen. In some osteomas of the spongy type, a layer of bone lies under the periosteum (fig. 12). Beneath this layer, although young cancellous bone is present, it appears less vascular and more mature than in the type lacking a layer of sur-

Fig. 7 (case 6).—Low power photomicrograph of the eburnated edge of a spongy osteoma. Small quantities of new bone are being laid down subperiosteally on the surface of cortical bone in the upper left hand portion of the picture. A few osteoblasts can be seen on the surface of the bone. Note the relatively anuclear appearance of the fibrous tissue in the extreme upper left hand corner.

face bone. It is important to note that the layer of surface bone at first is young in type and is actively being formed from preosseous tissue. It cannot, therefore, be the expanded outer table. There are osteomas which show intermediary stages of ossification between all the aforementioned types. It would seem, therefore, that they represent only different stages in the development of a similar process.

It should be mentioned that giant cell osteoclasts are seen scattered irregularly throughout the preosseous tissue in the spongy osteomas. In some places they are in apposition with bony spicules where they lie in little "lacunae."

As the result of trauma or some other less clearly understood stimulus, eburnated osteomas, which as a rule are small, in youthful patients appear able to take on a more active growth and hence are converted into a spongy form, which type comprises the majority of the
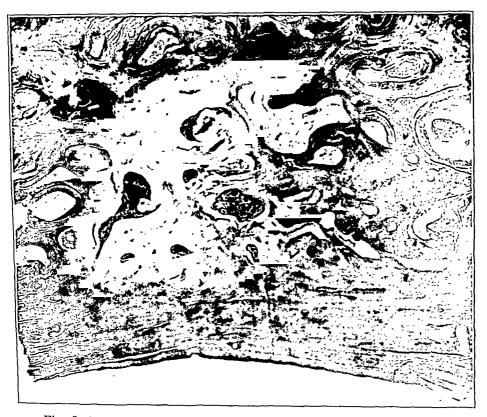
Fig. 8 (case 1).—A low power photomicrograph of an eburnated osteoma showing the smooth inner surface of the skull from which the endocranium has been stripped.

larger tumors.   In 1863, Virchow [7] recorded a similar observation. He recognized that certain cranial osteomas, originally of a porous nature, became eburnated in their later growth and were finally reconverted into a spongy form.   These observations have been largely neglected by more recent authors.

In the central regions of a spongy osteoma the microscopic picture is similar to that seen in most benign ossifying lesions, such as Paget's disease, ossifying periostitis and osteitis fibrosa or in the wall of a bone cyst.

HISTOGENESIS

In the foregoing analysis, much evidence was presented clinically, roentgenologically, grossly and microscopically that certain osteomas arise from preosseous tissue on the cranial surface and that these osteomas when actively growing are spongy and usually absorb the outer table of the skull, but when slowly growing or when the end-stages of ossification have been reached, they are eburnated and usually relatively quiescent. A review of the embryology and subsequent

Fig. 9 (case 7).—Low power photomicrograph showing the surface of a spongy osteoma. Hyalinized relatively anuclear fibrous tissue (periosteum) on the surface gives place in its deeper layers to adult preosseous tissue engaged in bone formation. The tendency for the spicules of new bone to be laid down in a peripherally radiating fashion is seen here at the surface of the tumor, but in its deeper layers they are laid down in an irregular fashion.

growth of the normal skull as well as the histogenesis of bone in general supports these observations.

It is generally accepted that the bones of the cranial vault and face (including the interparietal, parietal, frontal, squamous and tympanic bones, the median pterygoid plate of the sphenoid, the nasal, lacrimal and malar bones, the palatine, vomer, maxilla and a portion of the mandible) undergo intramembraneous ossification, being formed

directly from the mesenchymal blastoma without the intervention of cartilage, and that the other bones of the skull are preformed in cartilage and undergo endochondral ossification. From this it is evident that embryologically as well as histologically, as was shown in the microscopic sections, the osteomas of the cranial vault, which type comprised the great majority of this series, originate directly in pre-osseous tissue and not in cartilage, or precartilaginous connective tissue which is absent in this region. Although Cohnheim's theory of cartilaginous "rests" could possibly be advanced in connection with

Fig. 10 (case 7).—Photomicrograph showing a higher magnification of the surface of the spongy osteoma seen in figure 9. In the upper right hand corner is seen relatively anuclear hyalinized fibrous tissue (periosteum). This hyalinized fibrous tissue in its deeper layers shows a transition through a fibrospindle cell stage to preosseous tissue containing osteoblasts which in places are lined in rows along young trabeculae of new bone in the formation of which they are actively participating. Probable evidence that osteoclasis goes hand in hand with osteogenesis is supplied by the presence of a few giant cell osteoclasts applied to the new-formed body spicules.

osteomas having their origin in bones preformed in cartilage, it does not seem logical to apply it to those of the vault of the skull, nor, in fact, even to those of the temporal bone where no cartilage has been seen microscopically.

The fact that the normal membranous bones of the skull increase in thickness by a deposition of bone subperiosteally and in the outer table around the walls of the vascular channels directly from preosseous tissue with no intervening cartilaginous stage, accompanied by an internal reconstruction or absorption of old bony lamellae within, lends weight to this argument and presents a plausible site of origin for the osteomas, a site to which all evidence so far given in this paper has pointed.
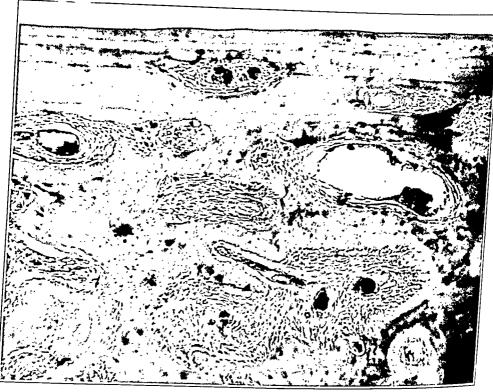
Fig. 11 (case 7).—Relatively high magnification of the inner table of the skull involved in a spongy osteoma. Note its partial spongy transformation, its smooth quiescent inner surface and the absence of endocranium (endosteum).

For almost two centuries a controversy has been in progress concerning the osteogenic function of the periosteum. In 1739, Duhamel,[11] in speaking of long bones, asserted that new bone was formed by the periosteum assisted by the endosteum. Since then he has had many followers, including Symes,[12] Flourens,[13] Ollier,[14]

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11. Duhamel, quoted from Haas.[16]

12. Symes, quoted from Haas.[16]

13. Flourens, Marie-Jean Pierre: Recherches sur le développement des os et des dents, Paris, Gide, 1842.

14. Ollier, Louis: Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux, Paris, V. Masson & fils, 1867.

Axhausen [15] and Haas. [16] Opposed to this theory of the osteogenic rôle of the periosteum there have been among others Haller, [17] Hunter, [18] Goodsir, [19] MacEwan [20] and Stump. [21] Additional complications are supplied by MacEwan, [20] who expressed the belief that the growth in diameter of the shaft of a bone is a result of interstitial growth of the bone itself. Stump, [21] in 1924, presented evidence that the periosteum is an end-differentiation of primitive connective tissue (mesenchyme) and that it serves only as a "limiting membrane," the growth in thickness of a bone resulting from subperiosteal osteoblasts and undifferentiated connective tissue cells (mesenchymal remnants) which are intimately blended with the deeper layers of the periosteum. MacEwan [20] previously formulated the theory that the periosteum functioned as a "limiting membrane" only.

Thus, if one can apply the foregoing theories to the development of the cranial osteomas, they may be regarded as arising either in the deeper layers of the periosteum or else subperiosteally, depending on one's definition of the word periosteum. It does not seem likely that they arise from interstitial growth in the surface of the outer table, but this cannot be disproved here. Microscopically, the hyalinized-like fibrous tissue on the surface of the osteomas appears in some cases (figs. 9 and 10) to give rise to elongated spindle cells, which in turn seem to develop into adult osteoblasts. From Stump's observations, however, it would seem rather that the hyalinized fibrous tissue was an end-product of the preosseous tissue underlying it.

The function of the outer layers of the periosteum as a "limiting membrane" is in part overthrown by these tumors in their outward growth. The fact, however, that they do not grow in an irregular manner but maintain a more or less smooth domelike shape is perhaps evidence of the presence of a partially "limiting membrane." On the other hand, the endocranium (outer dural layer), which is not involved in these tumors, appears to demonstrate more definitely its function as an internal "limiting membrane," by preventing any marked growth of the tumor toward the intracranial cavity. The resistance of this membrane, however, also frequently gives way before the severe pres-

15. Axhausen, George: Arch. f. klin. Chir. **88**:23, 1908-1909.

16. Haas, S. L.: The Importance of the Periosteum and the Endosteum in the Repair of Transplanted Bone, Arch. Surg. **8**:535 (March) 1924.

17. Haller, quoted from Haas. [16]

18. Hunter, John: Collected Works, London, James F. Palmer, 1837.

19. Goodsir, John: Anatomical Memoirs of John Goodsir, William Turner, 1868.

20. MacEwan, William: The Growth of Bone, Glasgow, James Maclehose & Sons, 1912.

21. Stump, C. W.: Histogenesis of Bone, J. Anat. & Physiol. **59**:136, 1925.

sure of an osteoma of the orbit or frontal sinus, as it does when an osteoma arises on the inner table.

Poirrier [22] suggested the possibility of the cranial sutures as a site of origin for these osteomas, but advanced no evidence in favor of this theory. The fact that active bone formation takes place in these

Fig. 12 (case 4).—High power photomicrograph of the surface of a spongy osteoma. A thin layer of young bone which extended over the surface of the tumor is seen in the process of being actively formed from preosseous tissue. Large osteoblasts are engaging in this work on the surface of the layer of bone. Relatively anuclear fibrous tissue (periosteum) lies on the surface of the tumor.

regions often until late in life certainly makes them a suspicious site, but although some osteomas may arise from them, others have been

22. Poirrier, A.: Des exostoses ostéogéniques de la voûte du crâne, Paris, 1895, no. 433.

definitely shown to arise far from the suture lines. Even if some osteomas do arise from the sutures, there is no evidence to disprove that they arise in the periosteal region in these locations.

In referring to the age incidence of these tumors, it was remarked that approximately 50 per cent of them arose before the patient was 8 years of age and about 75 per cent before the twelfth year. These observations prove of significance when the growth of the skull bones is investigated. In Quain's [23] book on anatomy is found the following:

The skull grows rapidly during about the first seven years of life. By that time certain parts including the circumference of the occipital foramen, the body of the sphenoid, the cribriform plate and the petrous portion of the temporal have attained their definitive size. The other regions also increase, but little, until the approach of puberty when a second period of active growth begins affecting especially the face and the frontal portions of the cranium, with which is associated the expansion of the frontal and other air sinuses—the frontal sinuses appear about the seventh year and continue to increase in size up to old age.

Since the large majority of osteomas arise during the active period of the growth of the skull, it is logical to believe that the production of these lesions is more favored in growing than in nongrowing bone. This early age of onset was noted in osteochondromas by Geschickter [6] and in the osteomas of the frontal sinus by Armitage,[24] who claimed that 50 per cent arise during adolescence. The literature seems to indicate that even more than 50 per cent of the osteomas of the frontal sinus arise before puberty, for although they may not be recognized until later, it is necessary to realize that they usually must attain a considerable size first.

The next question that confronts one is, Why should approximately 60 per cent of the osteomas involve the frontal bone and 50 per cent be almost totally restricted to this bone? It is known how comparatively common are the osteomas of the facial bones and of the frontal sinus of which Armitage [24] collected 119 from the literature. When one recalls that the frontal and facial bones continue to increase in size for a considerable time after many of the other bones have ceased to do so, and also that they show a special acceleration of growth about puberty, it becomes apparent that there may be some relation between these phenomena. Perhaps an osteoma in a bone which continues to grow actively for a long time is more likely to reach a larger size and hence to become clinically apparent than is an osteoma in a bone which grows sluggishly or ceases to grow at an earlier period. It is known that osteochondromas usually cease to grow when the bone of which they are a

23. Quain, Jones: Elements of Anatomy, ed. 10, edited by Schäffer and Thane, London, Longmans, Green & Co.; 1890-1895, vols. 1 and 2.

24. Armitage, George: Osteoma of the Frontal Sinus with Particular Reference to Intracranial Complications, Brit. J. Surg. **18:**565, 1931.

part ceases to do so, but unfortunately it is not known whether most of them would not have stopped growing regardless of whether the bone did so or not.

Another contributing factor is that if the production of an osteoma is more favored in growing bone then there is a longer period during which osteomas might arise from the frontal and facial bones than from bones ceasing to grow at an earlier date. The fact that the face and the frontal regions are perhaps more subject to trauma and that infection is more prevalent in these regions may also be factors in the production of the growths.

In the foregoing analysis, the osteomas appeared to arise either from the periosteum or subperiosteally on the surface of the skull. The larger osteomas were of the spongy type showing in their development a spongy transformation or absorption of the outer table and an eventual deposit of a layer of bone on their surface, and in some cases a quiescent end-stage or eburnated structure. Other osteomas, particularly those arising in adults, appeared to remain of a more or less eburnated character from the beginning. These phenomena are of particular interest when one consults those who have observed the healing of fractures. Although less callus is formed at the site of a fracture of a cranial bone and the union is more often a spongy one, the resultant process of healing is essentially similar to that in a long bone, when no intermediary cartilaginous stage occurs. In support of this, Dr. Dandy stated that he had observed solid bony union in some of his cranial osteoplastic flaps. At the site of a fracture, as is well known, after the original blood clot has been absorbed and replaced by granulation tissue, there occurs a formation of young bone trabeculae "which are first seen under the stripped periosteum in its angle of junction with the bone" (Leriche and Policard), and which spread out into the mass of fibrous tissue between the fractured ends of the bone to form a spongy callus. Coincident with the first of the foregoing phenomena, there occurs a process concerning which Leriche and Policard [25] wrote:

Biologically the most essential phenomenon, though histogenetically unobtrusive, is constituted by the slow but progressive resorption of bone at the extremities of the fracture. This resorption is manifested by the enlargement of the Haversian canals and of the connective tissue spaces. The bone disappears by osteolysis, much less than by osteoclasis. This disappearance always precedes the formation of new bone tissue. One can therefore say that the genesis of new bone trabeculae seems to be conditioned by the resorption of preexisting bone.

Here, then, is a probable explanation of the absorption or spongy transformation of the outer table as well as the inner table of the skull.

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25. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone: Its Problems, translated by S. Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

Following the foregoing stage in the repair of a fracture, there occurs a resorption of the spongy callus in its more central, areas with reformation of the medullary canal or diploe, a gradual formation of cortical bone continuous with the old cortical bone of the shaft or outer table and the return of the periosteum to its former relationship. This seems to explain the deposit of a bony shell over the spongy osteomas.

Concerning the healing of fractures, MacCallum [8] wrote: "The osteoid tissue may be laid down as a solid layer on the surface of the old bone or through the guiding action of the blood vessels assume a spongy form. Solid new formed tissue of this kind may be transformed later into spongy bone by the invasion of the blood vessels and that in turn become compact by later growth." Thus again is seen that the development of an eburnated or a spongy osteoma in part at least represents an exact replica of the normal growth of bone, but that some imbalance between the various processes concerned occurs with the resultant formation of an osteoma. From this it is not argued that all osteomas are due to trauma, although a fracture through the outer table with coincident imbalance of the factors concerned in repair could well explain their origin, as it is possible for the growth impetus to arise in the bone from many poorly understood sources, including periosteal infection. To say that these osteomas arise spontaneously is merely an admission that they arise from some obscure cause, as is also the case when one is forced to use the word imbalance.

Osteomas showing no clinical change in the outer table of the cranium occasionally extend toward the intracranial cavity from the inner surface of the skull and cause pressure on the brain. They apparently arise from the endocranium, or subendocranially. It is possible that osteomas may at times arise from the diploe, but no example of this type has been found.

The fundamental pattern of ossification observed in this study for osteomas of the cranium characterized by subperiosteal bony growth with accompanying spongy transformation of underlying bone is also typical for similar new growths arising in other membranous bones. A subsequent study of similar lesions of the jaws was suggested by Dr. Geschickter. This was undertaken (Geschickter and Echlin), and a similar histogenesis in so-called central fibromas and central fibrosarcomas, as well as osteomas, was demonstrated. These benign ossifying lesions, like the cranial osteomas, arise subperiosteally and are characterized in the roentgenogram by a spongy transformation of membranous bone extending outward from which is a smoothly outlined dome. On the surface of this dome is sometimes present a shell of newly formed bone. These growths often appear to be central because of the continuation of underlying spongy bone with the body

of the tumor as well as the presence of a bony shell on their surface.
This bony shell has often been mistaken for the expanded cortex of
the underlying bone. When the facts gathered from the study of the
pathology and histogenesis of cranial osteomas as reported in this paper
are considered from this larger point of view, including the similar
ossifying lesions in other membranous bones, it seems justifiable to
class the osteomas of membranous bones as a distinct entity different
from the exostoses (osteochondromas) in cartilaginous bones.

TREATMENT

Since many of the cranial osteomas grow slowly and remain small,
operative intervention is not always indicated. If a spongy osteoma,
however, is increasing in size, it seems wise to remove it and thus
avoid a possible thickening and slight depression of the inner table.

Unless osteomas are completely removed, they tend to recur. In
one case, however, although only the outer portion of the tumor was
removed, the inner table being left intact, the osteoma did not recur
except at one portion of its periphery (case 5).

HISTORICAL

Although isolated cases of osteomas of the cranial surface had
appeared in the literature prior to 1863, Virchow [7] in this year pre-
sented the first comprehensive work on the subject. He described the
osteoma as passing from an original spongy stage to an eburnated stage,
and finally perhaps to a spongy stage again. The spongy type, he
believed, showed a continuation of the cancellous bone with the diploe.
In speaking of osteomas of the skull in general, including osteomas of
the sinuses and orbit, he wrote, "and scarcely do they belong to a
single category, a part of them in my opinion belong to the enostoses,
another part to the exostoses and a third to the chondromata."

Prengreuber,[26] in 1892, believed that exostoses of the cranium were
never solitary, but coexisted with multiple exostoses.

In 1895, Poirrier [22] disagreed with Prengreuber. He deplored the
state of confusion that existed in the classification of these growths,
stating that until that time syphilitic, tuberculous and other lesions
were all included under the heading of osteomas. He believed that they
were solitary lesions independent of any other skeletal growth, but
that they were more frequent in the female sex. He thought some of
them might have arisen from the suture lines or from a wormian bone,
but gave no substantiating evidence in favor of these theories. He
wrote, "they are most common on the surface of the cranium and are
usually eburnated, but may pass through a cartilaginous stage." He

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26. Prengreuber, M., quoted by Marey.[9]

was quoting Virchow's theory of chondromas when he spoke of a cartilaginous stage, never having observed it himself. As has been pointed out, osteochondromas may rarely arise from cranial bones preformed in cartilage, but are quite different tumors from the osteomas described.

Marey,[9] in 1910, again stated that the osteomas of the skull had been somewhat neglected in the literature. He believed that "the cranial osteomata are not a pathological rarity. Contrary to the classical opinion, it is not a lesion occurring particularly in females and is able to co-exist with exostoses of the other bones." In his paper he included a case of Nageotte's which has been left out of this one. The patient, aged 15, since the age of 8 years had had exostoses of the frontal scapular and tibial bones with accompanying anemia and fatigue. Marey also wrote, "It seems legitimate to put in a group by themselves the spongy exostoses 'spongiostéomes' which are characterized by their faint density, their transparence in the x-ray and their tendency to develop not only toward the exterior, but also toward the interior of the cranium." He apparently believed that the spongiostéomes were a different type of lesion from the eburnated ones. He presented only one new case. The patient had a spongy osteoma, and epileptic seizures developed fifty-three years after the onset of the tumor. This case was included in the present study. It is true that in the spongy osteomas the inner table of the skull sometimes becomes transformed into spongy bone and slightly depressed, but in the foregoing analysis it was shown that the spongy and eburnated osteomas are only different manifestations of the same process.

Luxembourg[27] wrote a paper on this subject in 1918 and claimed that he was able to find little of value concerning the osteomas in the literature. Some of the osteomas in the literature he described as developing inwardly and outwardly. The only case with signs of increased intracranial pressure contained in his paper, however, was one reported by Hauff in 1846 and appeared to have been a hyperostosis over a meningeal fibroblastoma.

Orator,[10] in his paper in 1931, briefly reviewed the German literature on cranial osteomas and presented one new case. He concluded that the osteomas of the tabular bones arise early in life and are much more frequent in females than in males. He divided them into spherical and penetrating types, but did not recognize a transformation of one type into another, nor did he have anything to say concerning their origin. His own case he placed in the penetrating group. In the present paper it was grouped with the large spongy osteomas resting on a thickened and somewhat depressed inner table. In Orator's case

27. Luxembourg, H.: Beitrag zur Kenntnis der Osteome des Schädeldaches, Deutsche Ztschr. f. Chir. 147:256, 1918.

the neurologic examination gave negative results. The osteoma in one of his cases (previously reported by Eiselberg) apparently arose from the frontal sinus, and in another multiple osteomas were present.

In 1931, Armitage [24] wrote, "Osteomata of the frontal sinus as is almost invariably the case with bony tumors growing in connection with the cranial bones are of the hard, ivory compact variety—so-called exostoses eburnea." As was pointed out in this paper, the majority of the large osteomas studied were of the spongy type.

CRANIAL HYPEROSTOSES PRODUCED BY MENINGEAL FIBROBLASTOMAS

INTRODUCTION

The fact that meningeal fibroblastomas (meningiomas) frequently produce hyperostoses of the overlying cranium is now well recognized. The confusion that at times exists in the clinical and roentgenographic differentiation between these hyperostoses and the osteomas of the external surface of the cranium has prompted this portion of the paper.

With regard to the origin of the meningeal fibroblastomas, Penfield [28] wrote, "It must therefore be concluded that these tumors may arise from any portion of the meninges, but that they most frequently derive their origin from arachnoidal tufts, growing into and being vascularized by the dura." Concerning their subsequent growth, Cushing [29] remarked that they may form themselves into "massive tumors with a relatively small area of meningeal attachment" or into "tumors en plaque which are but slightly elevated, though they may involve a considerable area of dura."

Coincident with this growth there may occur changes in the overlying skull, evidenced first by a hypervascularization and then perhaps by a partial erosion or proliferation of new bone, "most striking on the internal and external surfaces of the skull, where it is easily distinguishable as layers of new bone superimposed on one another" (Kolodny [30]). Regarding the changes in the skull, Phemister [31] remarked "the inner and outer tables were slightly more spongy than normal. The new bone both internally and externally, radiated from the surface of the old bone." Cushing expressed the belief "that at least 25 per cent of the endotheliomas are accompanied by an overlying

28. Penfield, W.: Tumors of the Sheaths of the Nervous System, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 954.

29. Cushing, H.: The Meningiomas (Dural Endotheliomas): Their Source and Favoured Seats of Origin, Brain **45**:292, 1922.

30. Kolodny, A.: Cranial Changes Associated with Meningioma "Dural Endothelioma," Surg., Gynec. & Obst. **48**:231, 1929.

31. Phemister, D. B.: The Nature of Cranial Hyperostoses Overlying Endothelioma of the Meninges, Arch. Surg. **6**:554 (March) 1923.

hyperostosis cranii which is either palpable externally or demonstrable by the roentgen ray."

A microscopic examination of the hyperostosis resulting from this process, as has been revealed by all the foregoing authors, shows in most cases that it has been passively infiltrated with the cells of the meningeal tumor.

In speaking of the hyperostoses, Phemister [31] wrote:

In the second case nervous symptoms were entirely absent and the hyperostosis was the sole complaint. Such cases as the latter have not infrequently been diagnosed as sarcoma or osteoma of the skull and the underlying tumor overlooked. This has happened even when evidences of brain compression were present as the internal hyperostosis was held responsible for the compression.

CLINICAL FEATURES

An analysis of the most important clinical features in patients with hyperostoses overlying meningeal fibroblastomas is presented. The analysis is made from a review of nine cases of hyperostoses produced by meningeal fibroblastomas found in this laboratory and eighteen similar cases reported in the literature and is constructed with the view of differentiating between these tumors and the osteomas previously discussed. Of the nine cases found in the laboratory, only five presented clinically recognizable hyperostoses; in the other four these were found at operation. The cases taken from the literature were not selected, but all the cases presented in the articles of Phemister,[31] Penfield,[32] Cushing,[33] Rand,[34] Cope,[35] Winkelman,[36] and Crowe and Jones [37] were used.

Seventeen patients in this series were males and ten were females. The age of the patient when the meningeal tumor first manifested itself is given in twenty-five cases. The average age of these patients was 31 years, only four of them being under 29 years at the time of onset of signs or symptoms. The patient presented by Crowe and Jones was 5 years of age when a bony tumor of the frontal bone was noted. It

32. Penfield, W.: Cranial and Intracranial Endotheliomata, Surg., Gynec. & Obst. **36**:657, 1923.

33. Cushing, H.: The Cranial Hyperostoses Produced by Meningeal Endotheliomas, Arch. Neurol. & Psychiat. **8**:1 (Aug.) 1922.

34. Rand, C. W.: Osteoma of the Skull: Report of Two Cases, One Being Associated with a Large Intracranial Endothelioma, Arch. Surg. **6**:573 (March) 1923.

35. Cope, Z.: Case of Frontal Endothelioma with Hyperostosis Cranii (Pacchionian Tumor?), Brit. J. Surg. **12**:794 (April) 1925.

36. Winkelman, N. W.: Hyperostosis and Tumor Infiltration of the Base of the Skull Associated with Overlying Meningeal Fibroblastoma, Arch. Neurol. & Psychiat. **23**:494 (March) 1930.

37. Crowe, S. M., and Jones, C. K.: Large Hyperostosis of Cranium Due to Arachnoid Fibroblastoma, Tr. Chicago Path. Soc. **12**:340 (June) 1927.

is possible that this patient had a cranial osteoma and not a hyperostosis overlying a meningeal tumor.

The average duration of signs or symptoms at the time of operation among these patients was five years.

Of the twenty-seven cases, the hyperostoses were reported as localized chiefly to the frontal bone in ten and to the parietal bones in four. In five cases the tumor was described as involving the frontoparietal region and in four cases, the temple or temporal fossa. In two of the four cases, the orbital plates became thickened with resultant unilateral exophthalmos. In the remaining four cases the tumor involved the vertex, the crown, the occipital and the temporo-occipital region, respectively. The fact that the majority of these tumors involved the frontal or parietal bones with the predominant number involving the frontal bone is perhaps significant, as will be pointed out later.

In fourteen cases, or approximately half of the total number studied, a symptomless hyperostosis presenting on the external surface of the skull was the first indication of disease noted by the patient. Only two of these patients were under 29 years of age when the hyperostosis first appeared, one being 24 and the other, the patient of Crowe and Jones, 5 years. It is in this group particularly that difficulty has arisen in making a differential diagnosis between a hyperostosis of the meningeal type, an osteoma, an osteogenic sarcoma and a hyperostosis of definite inflammatory origin. The average duration of the hyperostosis before symptoms arose in these fourteen cases was four years, but in four cases the bony tumor was the only manifestation of disease for over nine years.

The symptoms complained of by these fourteen patients after the appearance of the hyperostosis varied considerably according to the location of the lesion. Headache, often localized to the tumor, was the most common symptom. Pains about the lump, dizziness and failing vision were frequent. Partial hemiplegia developed in four of the cases, epilepsy in three and loss of memory with mental dulness in some cases, particularly in those in which the frontal lobes were involved. Unilateral exophthalmos was noted in two cases. In only one case was the patient operated on before symptoms arose, and this patient had had a large hyperostosis of the frontoparietal region for two years. The average duration of symptoms at the time of operation in this group was three years and of the hyperostosis eight years.

There are three other cases that could perhaps be included in the aforementioned group in which symptoms followed the appearance of hyperostosis. Hyperostosis developed in each of the three patients from one to two and a half years before operation, but one had had neuralgic pain in her head for seven years prior to operation, another a prominence of the left eye for ten years and the third pain in the right eye for ten years.

There were four patients in whom signs and symptoms of intracranial damage developed simultaneously with the appearance of hyperostosis, and finally, six with definite signs of an intracranial tumor in whom hyperostoses cranii were found only at operation or autopsy.

The hyperostoses varied in size from that of an acorn to that of a grape-fruit and were firmly attached to the skull, shading imperceptibly into it.   In most cases they were semispherical, smooth or slightly lobular and bony hard, but in four cases they could be slightly compressed.   Some tenderness on pressure over the bony boss was present in four cases.   Dilated vessels in the scalp were mentioned in a few instances, and in one case the scalp was not freely movable over the hyperostosis, having been invaded by tumor cells.

General physical and neurologic findings varied greatly according to the amount and area of cerebral damage.

ROENTGENOGRAPHIC FEATURES

Roentgenographic changes in the cranium, the result of its infiltration by the cells of meningeal tumors, have been discussed by Heuer and Dandy,[38] Cushing,[33] Phemister,[31] Rand,[34] Sosman and Putnam,[39] Kolodny,[30] Camp,[40] Elsberg and Schwartz [41] and many others.   The following brief description of these changes is included here to facilitate a comparison between cranial osteomas and hyperostoses produced by meningeal fibroblastomas and is mostly taken from the observations of the aforementioned authors.

As a result of a meningeal tumor, there may develop in the overlying cranium a hyperostosis, an erosion, a hypervascularization or a combination of all three processes.

When erosion of the skull is absent, the hyperostoses produced by these tumors are usually typical.   Roentgenograms of cross-sections of the hyperostoses show their essential features most satisfactorily.   Some excellent examples of this type are contained in the articles on this subject by Kolodny and Phemister, and similar features are borne out in the gross specimens presented by other authors.   Fully developed hyperostosis is largely formed by new bone of a spongy character, arranged so as to radiate outward from both tables of the skull (figs. 13 and 14).   The formation of new bone is usually more pro-

38. Heuer, G. I., and Dandy, W. E.: Roentgenography in the Localization of Brain Tumors, Bull. Johns Hopkins Hosp. **27**:311, 1916.

39. Sosman, M. C., and Putnam, T. J.: Roentgenologic Aspects of Brain Tumors: Meningiomas, Am. J. Roentgenol. **13**:1, 1925.

40. Camp, J. D.: The Roentgenologic Manifestations of Intracranial Disease, Radiology **13**:484, 1929.

41. Elsberg, C. A., and Schwartz, C. W.: Increased Cranial Vascularity in Its Relation to Intracranial Disease, Arch. Neurol. & Psychiat. **11**:292 (March) 1924.

Fig. 13 (courtesy of Dr. D. B. Phemister).—Roentgenogram of a cross-section through a hyperostosis produced by a meningeal fibroblastoma (meningioma). The outline of the skull is preserved, although the bone is spongy. Bone is seen to be laid down in two different planes; adjacent to the cranial tables it is deposited in strips parallel to the skull surface, thus preserving the skull outline; more peripherally, it radiates at right angles to the skull. Unlike the osteomas, bone is deposited on the intracranial surface of the inner table.
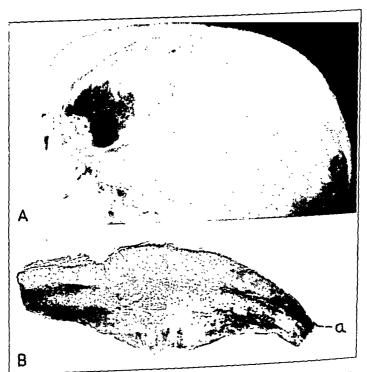
Fig. 14.—A (courtesy of Dr. J. D. Camp), roentgenogram of a hyperostosis caused by a meningeal fibroblastoma (meningioma). Spicules of bone are seen radiating from the outer surface of the frontal bone. The outline of the skull tables is faintly visible in the hyperostosis. New bone is present on the intracranial surface of the inner table. Stereoscopic plates should be used in order to more clearly visualize the inner table. Note the increased cranial vascularity.

B (courtesy of Dr. D. B. Phemister), roentgenogram of a cross-section of a hyperostosis produced by a meningeal fibroblastoma (meningioma). Note the widening and spongy transformation of the skull, the outline of which is well preserved. A large quantity of bone has been deposited on the under as well as the outer surface of the cranium.

nounced on the surface of the outer table than on the inner and presents a moundlike swelling passing at its periphery imperceptibly into the cranium. The outline of the cranium can be seen passing through the tumor. Concerning the hyperostosis, Kolodny [30] wrote, "even in the advanced cases of cranial changes, one may easily distinguish the outlines of both tables microscopically as well as in a radiogram of a slice of the removed bone flap. Destruction of the new formed bone on the intra-cranial side of the skull may lead to irregular, jagged excrescences of bone surrounded by soft tumor."

In a fully developed hyperostosis, although the outline of the cranium persists, it is usually widened both inwardly and outwardly, shows a spongy transformation with increased porosity and is rather hazy at the margins of the old tables. In contrast with the osteomas, the reason why the outline of the skull is still visible, even in the presence of a spongy change, is that new bone can be seen in the roentgenograms of some of the cross-sections of the hyperostoses to be laid down in two different planes. Proximal to the old skull tables the bone is laid down in layers parallel to the cranial surface, but more peripherally it is laid down at right angles to it (figs. 13 and 14 B). Microscopically this method of new bone formation is even more apparent.

In the early stages of development of a hyperostosis, and sometimes in elderly people, the skull may show only a slight thickening with no new bone radiating from it. The original thickening is the result of the deposit of bone in layers parallel to the surface of the skull. Below it one sees that the radiating spicules occur as soon as the periosteum is more completely stripped from the skull. Erosion of the skull sometimes takes place from within outward, either before or after the occurrence of hyperostosis (fig. 15). Hypervascularization, evidenced by widening of the haversian canals, is very common. Heuer and Dandy, as early as 1916, described some excellent examples of this type. Calcification is occasionally seen within the intracranial tumor, but this is apparently rare. A tumor of the soft part with perhaps an irregular layer of new bone on its surface can sometimes be visualized overlying the hyperostoses and at times may be the predominant feature (fig. 16). In some cases the meningeal tumor melts away the overlying skull like ice and presents as a firm, outwardly pulsatile swelling through the cranium. Dandy recently had such a case. Penfield [28] placed this type of meningeal tumor in the sarcoma group. Craig [42] endeavored to grade meningiomas according to their invasive properties, but this question will not be discussed here.

42. Craig, W.: Malignant Intracranial Endotheliomata, Surg., Gynec. & Obst. 45:760, 1927.
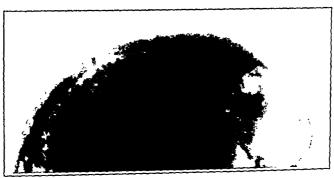
Fig. 15 (path. no. 45782).—Roentgenogram of a hyperostosis produced by a meningeal fibroblastoma (meningioma). Note the spicules of bone radiating from the surface of the skull. The outline of the cranium can be seen passing through the tumor. Some new bone is present on the under surface of the inner table, best seen on stereoscopic examination. Note the increased cranial vascularity and skull erosion.
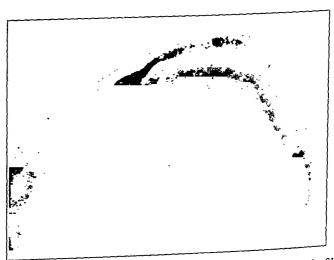
Fig. 16 (path. no. 37883).—Roentgenogram of a meningeal fibroblastoma (meningioma) presenting on the surface of the skull. New bone formation under the elevated periosteum is seen where the edge of the tumor merges into the skull. An irregular interrupted layer of bone is laid down on the tumor surface. A few thin strips of new bone are laid down at right angles to the skull parallel to the vessels in the tumor. Little or no bone radiates from the outer surface of the skull. The outline of the skull is well preserved. This patient was 54 years of age. A tumor had been present on the surface of his skull for eight years before the film was taken. This tumor can be easily distinguished from an osteoma by the intactness of the outer table of the skull, etc. The tumor was somewhat compressible.

GROSS PATHOLOGY

The gross specimens of the hyperostoses cranii over meningeal fibroblastomas reveal that bone described as radiating from the two tables is of the spongy type and is usually most abundant on the surface of the skull. In a few cases, and particularly in those in which erosion of the skull has commenced, little or no bone is found projecting from the inner table, but the rule, however, appears to be for it to do so when hyperostosis of any appreciable size is present. The cranium itself is also of a spongy nature when the hyperostosis is large, but its outline nevertheless persists.

Attached to the meninges beneath the hyperostosis lies the meningeal fibroblastoma which is invading the skull. It may either be of the spherical type with a small area of meningeal attachment or lie *en plaque* and be attached to the meninges over a considerable area. Although these tumors invade the skull, they are inwardly encapsulated, and usually destroy the brain only by pressure.

"On the outer surface of the bone is usually a pad of tumor," which "sometimes invades the overlying scalp and may infiltrate the temporal muscle when that is adjacent" (Penfield [28]). At times there may be little or no hyperostosis, but an enormous semispherical tumor of meningeal origin may lie on the surface of the skull (fig. 16).

MICROSCOPIC FEATURES

Microscopically, these hyperostoses are found to be infiltrated with the cells of the meningeal fibroblastoma to a greater or less extent. It is largely due to the infiltration of the skull by the cells of the meningeal tumor that hyperostoses are formed. These cells in their proliferation extend through the haversian canals and intertrabecular spaces toward the surface of the skull and in some cases show infiltration of the overlying scalp.

In most cases toward the surface of both tables and particularly toward that of the outer one, new trabeculae of bone are seen to be laid down in strips, parallel to the surface of the skull (figs. 17 and 18). The area of cranium involved shows a widening of the haversian canals and intertrabecular spaces, which at times is marked and gives this portion of the hyperostosis a definite spongy appearance. In the early cases the skull may show considerable infiltration with tumor cells and yet may retain a bony structure approximating the normal. This is apparently not common, however, as the increased cranial vascularity, which is usually present, will, in itself, cause widening of the haversian canals and intertrabecular spaces with resultant additional porosity.

In a fully developed hyperostosis there is seen radiating from both surfaces of the portion of the hyperostosis described, namely, the cranium proper and especially from the outer surface, trabeculae of
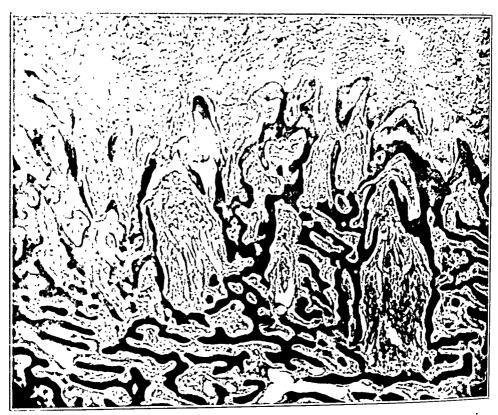
Fig. 17 (path. no. 45483).—Photomicrograph of the surface of a hyperostosis produced by a meningeal fibroblastoma (meningioma). Note that new bone is laid down in two distinct planes. The bony spicules in the lower part of the picture lie parallel to the surface of the skull and cover a much wider area than is seen here. Note the tendency for the meningeal tumor to be arranged in cords.

Fig. 18 (path. no. 45483).—Photomicrograph of the inner table of the skull involved in the hyperostosis shown in figure 17. Note again that bone is laid down in two different planes. Bone radiates at right angles from the inner table into the intracranial cavity.

new bone arranged more or less at right angles to the plane of the surface of the skull (figs. 17 and 18). Extending outward as a prolongation of the newly formed trabeculae are delicate bundles of pink-
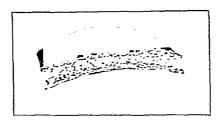
Fig. 19.—Roentgenogram of a cross-section of an eburnated osteoma arising on the cranial surface. This osteoma was recently found and was not previously mentioned in the paper. It was removed at autopsy from the parietal bone of a man, aged 66, who died from other causes.
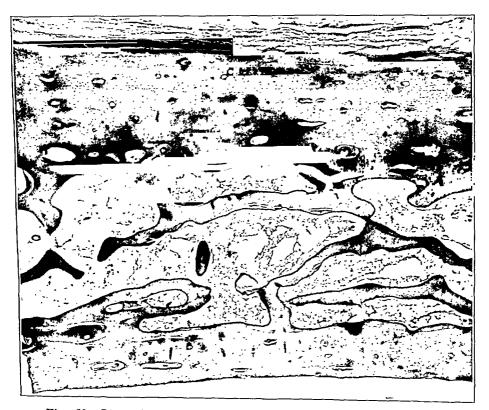
Fig. 20.—Photomicrograph of a cross-section of normal skull. Note the hyalinized periosteum on the surface of the skull. The outer table is thicker than the inner one. Compare this figure with the other photomicrographs.

staining fibers, identical in appearance to those observed by Quain [23] in ossifying embryonic membranous bone. (Compare the foregoing sections with figure 20, a microscopic section of a normal skull.) Cells

of the meningeal tumor lie between the newly formed trabeculae, and a pad of tumor is always formed on the surface of the outer table before trabeculae radiate from it.

There is no absolute line of demarcation between these two areas where bone is laid down in different planes, and this accounts for the haziness seen at their junction in the roentgenogram. These findings, however, explain why the outline of the cranium persists, even though it has undergone spongy transformation; and demonstrate one of the essential characteristics which clinically differentiate this type of hyperostosis from the cranial osteoma, in which, since the bone is not laid down in different planes, the outline of the skull proper is lost in the tumor. Normal-appearing osteoblasts always participate in the formation of the new trabeculae.
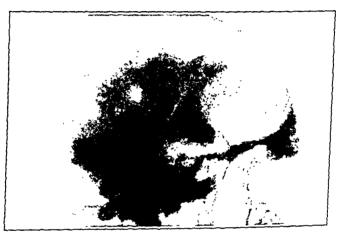
Fig. 21.—Roentgenogram of an osteoma arising within the frontal sinus. Note that this type of osteoma tends to fill the frontal sinus.

For a detailed description of the microscopic features of meningeal tumors, one may consult Penfield,[28] Cushing,[43] Weed,[44] Mallory,[45] Ewing[1b] and others. Here it is sufficient to say that the tumor cells are irregularly round or oval, sometimes being elongated, and that the nucleus contains abundant chromatin arranged in a netlike formation. The cytoplasm of the cell is voluminous, but the boundaries are usually indistinct. The cells resemble those seen in the pacchionian granulations and are often arranged in whorls, columns or clumps. In the

43. Cushing, H., and Weed, L. H.: Studies on the Cerebro-Spinal Fluid and Its Pathway: IX. Calcareous and Osseous Deposits in the Arachnoides, Bull. Johns Hopkins Hosp. 26:367, 1915. Cushing.[29]

44. Weed, L. H.: The Cells of the Arachnoid, Bull. Johns Hopkins Hosp. 31: 343, 1920. Cushing and Weed.[43]

45. Mallory, H.: The Type Cell of the So-Called Dural Endothelioma, J. Metab. Research 41:349, 1920.

center of the whorl is frequently seen a hyalinized blood vessel, a clump of collagen, or a psammoma body (corpora amylacea). A fibrous tissue stroma may be scanty or abundant.

COMMENT

Leriche and Policard,[25] who have made an extensive study of the normal physiology of bone, throw some light on the changes observed in the skull as a result of increased vascularity which is so often an accompanying feature of meningeal tumors. They expressed the belief that "if by any process whatever, the activity of the circulation is increased in the vicinity of a bone, the latter becomes rarefied. It changes neither in chemical composition nor in its fundamental histologic structure. It changes only quantitatively in the relation to that of the connective tissue. The medullary canals increase and the bone trabeculae diminish. The architecture of the bone is modified, but not the chemical structure of the bone substance present in the tissue; in the bone trabeculae which remain, the structure and composition are the same; only the size and number are diminished." This rarefaction of the skull accompanying an increase in circulation has been observed by most authors who have studied the meningeal tumors, but it has not been so adequately explained as by Leriche and Policard.

They also wrote, "In some instances, the exact rôle of the circulatory activity may be masked. An increase of the circulation leads to bone resorption, but through the freeing of calcium and the creation of a local calcific excess, new bone can be formed. There will then be histological atrophy of the bone tissue and anatomical hypertrophy of the bone as a whole. This double process in hypertrophic resorption is extremely frequent. It dominates bone pathology. . . ." This last observation to some degree supports Kolodny's [30] belief, but in no way proves it, that "proliferation of bone precedes the infiltration of the bone by tumor cells. This proliferation follows on the heel of a local dilatation of the vascular channels in the skull." Later it is shown that although some thickening of the skull may be due purely to a hypervascularization of the bone, the majority of the hyperostoses are a direct result of invasion of the tumor.

It was noted in the roentgenograms and microscopic sections that new bone in the hyperostoses was laid down in two different planes. Other authors have observed this method of new bone formation in the hyperostoses, but have not sufficiently explained its mode of origin, nor have they noted that this is the main reason why the outline of the skull is preserved.

It is well known that the skull normally increases in thickness by "successive depositions of bony lamellae under the periosteum" (Quain [23]), and that a similar deposition of bone in layers parallel to the

surface of the cranium occurs when the periosteum "suffers minute elevations." This is just what happens when the meningeal tumor grows through the outer table of the skull and causes a periosteal elevation. The endocranium of the inner table at a later date also becomes stripped from its attachment when the tumor in its proliferation grows inward as well as outward. This perhaps explains in part why the hyperostosis is smaller on the inner table of the skull as the tumor cells first have to reach a subendocranial (subendosteal) location and then later in their multiplication grow down toward the intracranial regions. Another reason is that the periosteum (or subperiosteal tissue) is a more active bone-forming organ than the endocranium (or subendocranial tissue).

After the tumor cells have passed through or more completely stripped the periosteum from its attachment, a vascularized fibrous tumor of meningeal origin is formed on the surface of the skull. Into this tumor, small spicules of bone radiate at right angles from the surface of the skull as previously described. This type of ossification is explained by Geschickter and Copeland [6] in their discussion of Ewing's sarcoma of bone. They stated:

Due to the growth of the tumor and subsequent hemorrhage, there is a gradual separation of the periosteum from the underlying cortex. Parallel deposits of new bone appear as a result of proliferation of the peripheral layer of the cortex when the periosteum has suffered minute separation. With increased separation of the periosteum, spicules of new bone from the subperiosteal regions are laid down at right angles to the shaft rather than parallel. We agree with Ribbert that this is due to the blood vessels perforating Volkmann's canals. After the separation of the periosteum, these vessels determine the direction of the new growth of bone when they are pulled outward in maintaining their continuity. The two types of formation of bone parallel and radiating, duplicate the process observed in the embryo, etc.

The same mode of new osseous deposit is seen to a lesser extent on the inner table, and the explanation for this is apparently similar.

Phemister,[31] in his paper on the hyperostoses under discussion, expressed the belief that "whether it [the new bone formation] arises from tumor cells or from the old bone, it is arranged to support the tumor." In support of this view, one may consult Phemister's article as well as Quain's [23] study of the growth of membranous bone. Quain said, "It may be observed that the appearance of the ossifying membrane bone in the shape of a network of trabeculae, seems to be determined by the preexistence of a vascular network in the embryonic tissue. The new bone everywhere makes its appearance in the spots which are furthest from the vessels, and the bony network everywhere alternates with the vascular network." Thus the radiating arrangement of the new bone formation is probably determined by the preexisting

vascular structure of the meningeal tumor which radiates from the surface of the skull (fig. 16).

Phemister [31] is also of the opinion that "the new bone (in the hyperostosis) is not tumorous in nature and is merely ossified stroma of the invading endothelioma." This opinion seems logical, especially perhaps in the light of experiments performed by Leriche, Policard and others, who have shown that any fibrous connective tissue in an embryonic state, when in apposition with bone, may undergo ossification if there is produced ·by hypervascularization and consequent rarefaction of the adjacent bone a local excess of calcium. Although Phemister's theory is logical, it must be remembered that some of the new bone formation in the hyperostosis is undoubtedly of periosteal or subperiosteal origin (fig. 16).

Another question that deserves consideration is, Why should so many of the hyperostoses involve the frontal bone? It has been shown by other authors that the majority of meningeal tumors arise from the meninges over the vault of the skull, and this has been explained by their possible origin from the pacchionian granulations, which are so frequent in this region. Although many meningeal tumors arise in regions nearer the base of the skull, hyperostoses in these regions are apparently very infrequent. It will be remembered that osteomas show a tendency to develop in growing bone. Hyperostoses may show this same tendency. In support of this supposition is the fact that the frontal bone not only continues to grow after many of the other bones have ceased to do so, but also shows a more active growth in later life than the other cranial bones. The parietal bone, which is also frequently involved, is likewise among the bones that continue to grow after many of the others have ceased to do so. It does not, however, show such an active growth as the frontal bone in later life.

DIFFERENTIAL DIAGNOSIS [46]

There are many essential differences between the benign osteomas of the outer surface of the cranium discussed in this paper and the hyperostoses produced by meningeal fibroblastomas, and although difficulty at times will be encountered in distinguishing between them, their differential diagnosis should as a rule be easy.

Evidence of increased vascularity and of erosion so frequently seen in the skull over meningeal tumors is an uncommon accompanying feature of osteomas. A spongy osteoma, however, occasionally appears to erode the skull, but this is due to its spongy nature. A lateral view of the tumor is therefore always indicated. Hyperostoses are more

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46. The osteomas referred to in the first part of this differential diagnosis are, of course, the osteomas described in detail in this paper, namely, those that arise from the periosteal region on the cranial surface.

often tender than osteomas, and sometimes present a pad of tumor on their surface. Meningeal tumors frequently cause severe intracranial damage, but osteomas rarely do so. In a hyperostosis, the outline of the cranial tables persists. In an osteoma of any appreciable size, the outer table is absorbed. Bony spicules which so commonly radiate from both surfaces of the skull in the hyperostoses are only occasionally seen near the surface of the dome of an osteoma and rarely if ever radiate from the inner table underlying it. Apart from these general differences between the two tumors, osteomas show certain special differences according to the stage of their development.

The fact that osteomas usually arise before or about puberty, whereas meningeal tumors are most frequent in the fourth decade of life, eliminates more of the difficulty in differentiating between these two lesions. Rarely, however, osteomas occur in adults, but in these cases the tumors unlike the hyperostoses are more often eburnated, show a dense shadow in the roentgenogram and produce no radiating bony spicules from the inner or outer tables of the skull.

The spongy osteomas of long duration should give little trouble in diagnosis, as again, unlike the hyperostoses, they usually arise in youth or in infancy, show an absorption of the outer table of the skull, some depression and thickening of the inner table, but no new bone radiating from it, and frequently have a thin shell of bone on their surface.

The spongy osteomas may early in their growth show spicules of new bone radiating from the surface of the skull in a manner similar to that seen in the hyperostoses cranii. Since these osteomas apparently originate in the periosteal region, the inner table of the skull in their early stages should show no change from the normal. In the formation of a hyperostosis, the meningeal tumor usually causes an increased porosity of the inner table or the production of spongy bone radiating from it. A stereoscopic film should, therefore, be of value in distinguishing between the two lesions. The other points of differentiation mentioned should, as a rule, decide the diagnosis.

The thickening of the skull, which occurs in a hyperostosis before the formation of radiating spicules, may give a little difficulty, however, if the diagnosis is based on this criterion alone.

Low grade osteomyelitis of the skull may sometimes simulate either of the foregoing tumors, but in the roentgenogram the irregular areas of bone destruction with adjacent areas of sclerotic bone are usually typical.

Primary sclerosing osteogenic sarcoma may be recognized by the rapidity with which it produces a large area of bone destruction and irregular new bone formation. The radiating manner in which new bone is sometimes laid down occasionally resembles closely that seen in a hyperostosis fo meningeal origin. Other primary tumors of the

skull as well as metastatic ones are generally much more rapidly grow-ing than osteomas or hyperostoses of meningeal origin. Most of them are destructive. The benign giant cell tumor, if subperiosteal in origin, is usually soft. If it arises in the diploe, it produces an expanding and destructive lesion.

The characteristics of osteochondromas of the cranial surface were pointed out (fig. 1). Osteochondromas growing intracranially are often hard to visualize in the roentgenogram and cause compression of the brain.

Osteomas of the orbit and frontal sinuses may in their growth cause a swelling of the frontal bone, but the fact that these tend to fill the orbit and frontal sinuses, respectively, differentiates them from the osteomas of the cranial surface which never do this (fig. 22). Osteomas arising from the inner table of the cranium usually cause early damage to the brain and rarely if ever produce a demonstrable clinical change in the outer table. Exostoses of syphilitic origin are frequently multi-ple and usually disappear rapidly with antisyphilitic treatment.

A biopsy is indicated when any doubt exists as to the nature of a cranial tumor.

CONCLUSIONS

1. The osteomas discussed in this paper may be either spongy or eburnated, and arise from preosseous tissue on the cranial surface, as a rule, early in life. They grow slowly and most frequently take origin from the frontal bones, although other cranial bones are also commonly involved. They usually, if not always, arise in growing bone.

2. In its growth the spongy type of osteoma usually causes an absorption or spongy transformation of the outer table of the cranium and becomes continuous with the diploe. As a result of this process, the inner table of the skull in the region of the tumor may become slightly depressed and thickened, but rarely sufficiently, unless a com-plicating factor is present, to cause compression of the brain. A layer of bone is sometimes laid down on the surface of the tumor. Micro-scopically, this bone is young in type and is being actively formed from preosseous tissue. It is not, therefore, as usually believed, the expanded outer table of the cranium. This type of osteoma has often been described as arising from the diploe.

3. The fundamental pattern of ossification observed in this paper for osteomas of the cranium, characterized by subperiosteal growth, with accompanying spongy transformation of underlying bone and the frequent deposit of a subperiosteal shell of new bone, is also typical for similar new growths arising in other membranous bones.

4. Osteomas of the cranial surface rarely arise in adults, and then tend to be of the dense eburnated type.

5. Osteomas of membranous bones are a distinct entity from exostoses (osteochondromas) in cartilaginous bones.

6. Hyperostoses produced by meningeal fibroblastomas can be distinguished from osteomas of the cranial surface prior to operation.

Osteomas usually arise in youth and hyperostoses in the fourth decade of life. Compression of the brain, so commonly an accompanying feature of hyperostoses, is rarely caused by osteomas unless some complicating factor is present. Hyperostoses are more frequently tender than osteomas and unlike osteomas are sometimes compressible.

The roentgenographic differences between these two bony growths are distinctive.

7. In the formation of a hyperostosis, ossification adjacent to the tables of the skull occurs in parallel strips under the periosteum and endosteum when these tissues are minutely elevated by the meningeal tumor in its growth. When these tissues become more completely stripped from their attachments, new bony trabeculae are laid down at right angles to the cranium, the direction of their deposit apparently being determined by the radiating vascular arrangement of the meningeal tumor. This deposit of trabeculae in two different planes explains why the outline of the cranium persists in the hyperostosis.

In the region of a meningeal fibroblastoma a small amount of thickening of the skull may result purely from hypervascularization, but the production of a hyperostosis of any appreciable size is apparently always due to the infiltration of the skull by the cells of the meningeal tumor.

8. Osteomas that cause severe pressure on the brain usually arise either about the paranasal sinuses or the orbit or from the inner surface of the skull and not in the periosteal region on the cranial surface.

REPORT OF CASES

CASE 1.—*History.*—A white man, aged 28, was admitted to Dr. Dandy's service on Sept. 8, 1920, complaining of a lump on the forehead. The family and personal histories were irrelevant.

At the age of 5 years, the child's parents noted a small lump in the center of his forehead about the size of a ten cent piece. This remained practically stationary until eight years before admission, when, as a result of trauma, it grew rapidly, reaching three times its former size in a few days. The tumor was incompletely removed in 1912 and 1914. It then recurred and grew slowly. There were severe headaches in the afternoon for several years, and a sense of pressure in the region of the tumor for a short period.

Physical Examination.—The patient was well nourished. The temperature and pulse were normal. The forehead presented an old postoperative scar in the midline under which was an uneven but smooth, rounded, bony hard, nontender mass, 8 by 3 cm. and protruding 1 cm. from the skull. The eyegrounds were normal. The general physical and neurologic examinations gave negative results.

There were 8,000 white blood cells and 100 per cent hemoglobin. A culture from the frontal sinuses taken at operation showed no growth.

Operation (Dr. Dandy).—The osteoma was removed with a surrounding margin of normal bone. Both frontal sinuses were opened, but appeared perfectly normal, except for enlargement. In the opinion of the operator, "the osteoma was probably due to a chronic inflammatory condition of the frontal sinuses."

The diagnosis at the time of operation was osteoma of the frontal bone, probably arising from the frontal sinus.

Gross Pathology.—The specimen consisted of a piece of bone, 7 cm. long, projecting from the flat outer surface on which were two rounded lumps fusing together. These were of bony consistency and fused imperceptibly into the surrounding skull. The undersurface of the inner table of the skull was smooth, and showed the median longitudinal ridge and no evidence of new bone formation.

Microscopic Pathology.—The section through the tumor showed a surface layer of hyalinized fibrous tissue with a layer of underlying cortical bone, which in turn fused with a zone in the center of the tumor of cortical bone showing wider intertrabecular spaces, and this finally gave place to a layer of cortical bone or inner table of the skull. The inner table was smooth and normal in appearance. There was no evidence of new bone formation in the section.

Ultimate Result.—Up to 1929, there had been no recurrence of the tumor, but the patient had had chronic frontal sinusitis.

CASE 2.—*History.*—A white man, aged 33, was admitted to the service of Dr. Dandy on June 12, 1920, complaining of a lump on the forehead. The family and personal histories were irrelevant.

In 1909, the patient was struck on the forehead by a pointed metal spike which penetrated the skin; the wound healed rapidly. In 1915, a lump appeared at the identical spot of the trauma and reached its present size in six months, but then remained practically stationary. The patient could feel a dent in the tumor at the site of the old trauma for some time. There were no symptoms referable to the tumor and no headaches, changes in vision or neurologic symptoms.

Physical Examination.—The patient appeared healthy; the temperature and pulse were normal. On the forehead, just over the left orbit, was a bony, hard, smooth, regular, nonmovable, nontender tumor, the size of a walnut. The skin over the tumor was freely movable and appeared normal. Pressure over the left frontal sinus disclosed slight tenderness. The remaining examination, including a neurologic examination, gave negative results. The Wassermann reaction was negative.

Operation (Dr. Dandy).—The tumor was chiseled off level with the skull. "It was bone, quite spongy with wide interstices." A wide margin of normal bone, including the inner table, was then removed.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—The gross specimen consisted of three pieces of bone, each made up of a mass of cancellous bone and fibrous tissue with an overlying definite layer of fibrous tissue.

Microscopic Pathology.—The section through one of the pieces of bone showed a layer of hyalinized fibrous tissue on one surface. This fibrous tissue showed a gradual transition through a spindle cell stage to a definite preosseous tissue in its deeper layers. The preosseous tissue was very vascular and was actively laying down young cancellous bone.

Ultimate Result.—The patient was discharged well. On Oct. 30, 1931, he was reported well.

CASE 3.—*History.*—A white woman, aged 20, was admitted to the service of Dr. Dandy on May 25, 1921, complaining of headaches, a lump and pressure on top of her head. The family and personal histories were irrelevant.

At 1 year of age, she fell down a stairway and fractured her skull with immediate resultant internal strabismus and partial loss of vision in the left eye. Since then, she had had a lump on the right side of her head which grew slowly, but never showed any rapid increase in size. Following a "nervous break-down" three years before admission, she had a sense of pressure on top of her head. Tenderness over the lump was present for a few years, and for two months she had had severe pain and headaches beneath the tumor. Slight weakness of the left side had been present for some time. There was no vomiting.

Physical Examination.—The patient was a well nourished and intelligent woman. On the right side of the head at the junction of the frontal and parietal bones, encroaching on the midline and extending laterally for 8 cm., was a bony prominence, extremely hard and very tender near its lower margin. No cracked-pot sound was noted over the head. The vision was poor in the left eye, and the right disk was slightly injected. There was internal strabismus in the right eye, the tongue protruded slightly to the right, and there was slight weakness of the left arm and leg with exaggerated deep reflexes on the left. The remaining examination was negative. There were 6,020 white blood cells and 72 per cent hemoglobin.

Operation (Dr. Dandy).—Two openings in the vault of the skull were present. These were each 1 cm. in length, 0.5 cm. wide and about 3 cm. apart. The bone was extremely hard, but ragged, about the edges of these openings. Cerebrospinal fluid poured out through them. They were joined with rongeurs until a defect about the size of a silver dollar was made. Degenerated scarred cortex was seen. A large bone flap, the undersurface of which was slightly roughened, was then laid back. The dura was entirely lacking over the exposed area, and several round, smooth, apparently multilocular cysts containing clear fluid were present in the cortex. These were excised, and the bone flap was replaced. How much of the osteoma was removed is not known. Infection apparently played a part in this case.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—There was no report.

Microscopic Pathology.—The section showed a loosely arranged, very vascular fibrous connective tissue, containing a few irregularly scattered bony spicules. This section was taken from the edge of the tumor.

Ultimate Result.—The patient was discharged well. On April 23, 1922, she was reported well.

CASE 4.—*History.*—A white youth, aged 19, was admitted to the service of Dr. Dandy on Sept. 22, 1931, complaining of a bony tumor behind the ear. The family and personal histories were irrelevant.

A small bony tumor was removed from behind the patient's ear in 1919. This tumor recurred and was removed in 1927. It again recurred and grew slowly, especially perhaps during the year prior to his admission. It was never painful or tender. There was no history of headaches, interference with hearing or otitis media. No other symptoms were complained of.

Physical Examination.—The temperature and pulse rate were normal. Behind the right ear and pushing it forward was a bony hard, nontender, slightly irregular tumor, 3 by 3 by 2.5 cm., attached to the temporal bone. The center of the mass lay about 4.5 cm. above the tip of the mastoid. The skin was normal and freely movable over the tumor, but there was present an old operative scar. The Wassermann reaction was negative. The general physical and neurologic examinations gave negative results. There were 10,400 white blood cells and 100 per cent hemoglobin.

Operation (Dr. Warthen).—The tumor was composed of a cancellous dome and a more compact base. It was removed with a small area of surrounding normal bone from the inner table, which was left intact.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—A cross-section of the gross specimen consisted of several pieces of bone. On the surface of each was a layer of fibrous tissue, under which was a thin rim of fairly well calcified material and in the central portion what appeared to be cancellous bone.

Microscopic Pathology.—The section showed a layer of hyalinized fibrous tissue at the periphery of the section which passed through a fibrospindle cell stage and showed definite preosseous tissue in its deeper layers which was actively engaged in the formation of young, bony spicules. Underneath the surface layer of fibrous tissue was an almost continuous rim of young bone (being actively formed from preosseous tissue). Sections from the base of the osteoma showed a more quiescent picture and an abundance of adult cortical bone.

Ultimate Result.—The patient was discharged well.

CASE 5.—*History.*—A white boy, aged 13, was admitted to the service of Dr. Dandy on Feb. 16, 1923, complaining of an enormous bony tumor in the frontal region. The family history and personal history were irrelevant.

At 7 months of age the patient's mother noticed a small lump, "the size of a pea," on the vertex of the child's skull. The lump was hard and nonpainful. It grew slowly in size until the patient was 4½ years of age, and then grew more rapidly, especially in the two years prior to admission. No pain, redness or tenderness was noted. Two years before admission, the patient's mother noticed two small lumps on either side attached to the nasal bone. These increased gradually in size, causing obstruction to breathing. The child never went to school, owing to the appearance of the deformity. He was somewhat mentally retarded. He had an irregular fever for four weeks prior to admission, the cause of which was unknown.

Physical Examination.—The patient was somewhat undernourished and showed slight mental retardation (the fact that he had not been to school might partially explain this). An enormous, bony hard, slightly irregular and faintly nodular, pear-shaped tumor, measuring 19 cm. in its anteroposterior diameter and raised 6.5 cm. from the surface of the skull was attached to the frontal bone and extended backward to about the parietal suture line. Its anterior border involved the glabella of the frontal bone and the left supra-orbital arch. There was no cracked-pot sound over the skull, nor was there tenderness. The skin was normal. The tumor seemed to fade imperceptibly into the surrounding skull. A small tumor mass was attached to the nasal bones in each nostril. There was a slight bony, nodular and roughened area on the surface of the third rib in the midclavicular line. The fundi were normal. Neurologic and general examination gave negative results

except for two or three fibrous-like nodules in the skin of the face and ear. There were 8,100 white blood cells. The Wassermann reaction was negative. A culture from the frontal sinus opened at operation showed no growth.

Operation (Dr. Dandy).—The osteoma was chiseled away, leaving the inner table intact. The surface of the tumor was formed "by a thin layer of bone, not more than 0.25 cm. in thickness, and below this was cancellous bone. A perforator, passing through the cortex, entered soft mushy bone through which it plunged easily. The left frontal sinus was opened and leveled down. It was of tremendous size and protruded beyond the normal curve of the frontal region, but showed no sign of infection. The right sinus was not opened."

The diagnosis was osteoma of the skull.

Gross Pathology.—The gross specimen consisted of several pieces of bone, each showing a hard, cortical surface with underlying cancellous bone.

Microscopic Pathology.—The section showed a layer of thick fibrous tissue overlying a thin continuous layer of young bone. The central areas of the tumor were composed of preosseous tissue and irregularly arranged trabeculae of young bone.

Ultimate Result.—The patient was discharged well. On March 20, 1930, he was in good health, but thought that the tumor was recurring over the right eye.

CASE 6.—*History.*—A white girl, aged 18, was admitted to the service of Dr. Dandy on Feb. 5, 1928, complaining of a bony swelling of the frontal region.

Since the age of 6 years, the patient had had a lump on the forehead and on the bridge of the nose. There was an indefinite history of having fallen out of a tree at this time and striking her forehead. She also had had a lump on the vertex of the cranium since birth. Both lumps grew slowly and regularly in size. There had been no pain or other symptoms.

Physical Examination.—The patient appeared healthy. The temperature and pulse rate were normal. On the forehead just to the left of the midline was a smooth, rounded, bony hard tumor attached to the skull. It extended upward to within 2 cm. of the hair line. Another similar prominence saddled the nasion, and there was a third, the largest, on the skull, in the midline just back of the hair line which was about 6 cm. in diameter and 2 cm. high. All these masses fused into one another. The skin was normal and freely movable over them. They were nontender. The results of the general physical and neurologic examinations were negative. The Wassermann reaction was negative. There were 9,100 white blood cells and 95 per cent hemoglobin.

Operation (Dr. Hart).—A very firm cartilaginous-like tumor was dissected off from the bridge of the nose (the cartilaginous appearance was due to the thick fibrous tissue on the surface of the tumor). In attempting to remove the remainder of the osteoma, an enlarged frontal sinus was opened. The operation was abandoned.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—The gross specimen consisted of three small fragments of bone; each fragment was covered by a dense white fibrous tissue.

Microscopic Pathology.—On two edges of the section was seen dense, hyalinized fibrous tissue which in a few areas showed a gradual transformation to preosseous tissue in its deeper layers. This fibrous tissue overlay dense adult cortical bone which in places, however, was being added to from the areas of preosseous tissue mentioned. The center of the tumor was formed by dense, adult cancellous bone.

The picture in general was one of quiescence and that of an eburnated osteoma (this section was removed from the lower edge of the tumor and from the roentgenogram it can be seen that this is really a spongy osteoma, eburnated in its periphery).

Ultimate Result.—The patient was discharged well.

CASE 7.—*History.*—A white youth, aged 18, was admitted to the service of Dr. Dandy in March, 1929, complaining of an enormous bony tumor on the vertex of the skull. The family history and personal history were negative.

At the age of 4 years the patient fell and struck his left supra-orbital region. Ten years later, a small, bony tumor developed at the site of the trauma. At 5 years of age, he fell and struck the back of his head. A bony tumor was noticed at the site of this trauma when the patient was 7 years of age. The skin was not lacerated in either case. Both of these lumps gradually increased in size. At about 10 years of age, he was told that he did not have long to live, and since the age of 16 years had had several fainting spells, which were not accompanied by convulsions, aphasia, vomiting or incontinence. Apart from a sense of weight over the apex of the skull, there were no other symptoms.

Physical Examination.—The temperature and pulse were normal. A bony hard, rounded, nontender tumor about the size of a coconut was attached to the left parietal bone. Some dilated vessels were present over the tumor. A similar lump fusing with the one described, but having the shape of a saucer, was present in the left frontal region and shaded imperceptibly into the surrounding skull. The fundi were normal, and the results of the general physical and neurologic examinations and the Wassermann test were negative. There were 10,600 white blood cells and 104 per cent hemoglobin.

Operation (Dr. Dandy).—The osteoma was partially removed. There was considerable bleeding when the thickened vascular periosteum over the tumor was incised. The bone beneath was very vascular and of a soft, mushy, cancellous character. This type of bone extended inward to a quite firm inner table. The bone removed weighed 405 Gm. The majority of the osteoma was removed, including the inner table of the skull.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—The gross specimen consisted of a large domelike mass lying on the removed inner table of the skull. The surface of the dome was covered by a thick fibrous tissue. The body of the mass was composed of cancellous bone through which a knife could be easily plunged. No cortical bone lay on the surface of this tumor. The inner table showed no evidence of new bone formation on its intracranial surface and was smooth except for vessel markings.

Microscopic Pathology.—A section through the outer surface of the tumor showed on the surface a thick hyalinized-like fibrous tissue, giving place to definite preosseous tissue in its deeper layers which was actively participating in the formation of cancellous bony spicules. No cortical bone was seen on the surface of the tumor. Section through the inner table of the skull showed an intact inner table which, however, on its tumor side was transformed into spongy bone.

Ultimate Result.—The patient was discharged well.

Cases from the Literature

Case	Author*	Sex	Age	Age of Patient When Tumor First Noted	Duration in Years	Symptoms	Location on External Table	Gross Pathology	Microscopic	Treatment and Results
8	Chassaignac: Thèse de Concours, 1848	?	21	12	9	Symptomless bony hyperostosis which grew slowly at site of trauma; general physical and neurologic examinations gave negative results	Frontal bone encroaching on glabella	Eburnated, 3×1½ inches	....	Removed; discharged well
9	Wahl: Thèse de Dorpat, 1874	?	12	Infancy	?	Symptomless bony hard tumor, arising without apparent cause; general physical and neurologic examinations gave negative results	Right frontal bone above the orbit	Bony tumor, size of walnut	....	....
10	Karowski, 1894, quoted by Marcy °	?	7	Infancy	?	Symptomless bony hard tumor, arising without cause on skull; three other hyperostoses on face; general physical and neurologic examinations gave negative results	Superior frontal bone	Spherical, bony tumor with large base	....	....
11	Reclus: Presse méd., 1894, p. 351	F	21	?	?	Symptomless bony hard tumor	Frontal bone	Bony tumor	....	Removed
12	Prengrueber,³⁰ 1892	F	22	11	11	Symptomless bony hard tumor arising after trauma; general physical and neurologic examinations gave negative results	Left frontal bone	Bony tumor covered by periosteum, the size of a cherry	Periosteum on surface underlying cortical bone, central spongy bone	Removed
13	Demaye: Bull. Soc. anat. de Paris (3):841, 1894	F	33	22	11	Symptomless bony hard tumor arising without apparent cause; general physical and neurologic examinations gave negative results	Right frontal bone near inferior extremities of fronto-parietal suture	Large base, eburnated bony tumor, size of large walnut covered by periosteum	Normal looking bone continuous with diploe	Removed
14	Hott: Tr. Path. Soc. London, 1850-1851, p. 149	M	40	14	26	Bony hard tumor, apparently symptomless, arising after trauma	Left parietal bone	Broad-based, spongy bony tumor, 3×2 inches; normal inner surface of skull	....	....
15	Cooper: Lancet 1:628, 1861	F	23	19	4	Bony hard tumor arising without apparent cause; some tenderness was present	Just above mastoid bone	Eburnated bony hard tumor, size of large walnut	....	Removed
16	Textor: Würzb. med. Ztschr. 6:329, 1865	?	66	Infancy	66	Bony tumor, apparently symptomless, arising after trauma	Temporal bone	....	....	Died at 66 years of another disease
17	Macintre: Bull. Soc. anat. de Paris 7:67, 1905	M	29	28	1	Symptomless bony hard tumor; general physical and neurologic examinations gave negative results	Temporoparieto-occipital region	Bony tumor covered by thick periosteum with underlying osseous lamelae, continuous with mastoid cells	Osseous tissue on surface underlying cortical bone	Removed

Reference	Sex				History	Location	Tumor	Microscopy	Result
19 Millon: Bull. Soc. anat. de Paris, 7:72, 1905	F	25	Several years before patient was 15	Over 10 years	Symptomless bony hard tumor; general physical and neurologic examinations gave negative results	Temporomastoid bone	Eburnated osteoma, no communication with mastoid cells	....	Removed
19 Murcy, 1910	M	65	12	53	Bony hard tumor, symptomless until patient was 60 years of age, when irregular headaches and attacks of epilepsy commenced; no loss of consciousness; epilepsy arose after typhoid fever	Upper right parietal bone	Bony hard tumor, 37 cm. in circumference; roentgen evidence; tumor loss dense than other cranial bones; "spongiostéome"	....	No operation
20 Oesterlein: Wurtemb. med. Kor.-Bl., 1832, p. 79	M	76	31	45	Symptomless bony hard tumor arising after trauma; size of bean at onset; grew to size of grape-fruit; general physical examination gave negative results	Frontal bone	Eburnated..........	....	Removed
21 Bonnet, quoted by Luxembourg	?	..	..	..	Two bony hard tumors	Large one on frontal bone; small one on parietal bone	Irregular surface, spongy bone in center of tumor, inner table slightly depressed	....	....
22 Burns, quoted by Luxembourg	F	32	..	..	Bony hard tumor, apparently symptomless; had grown slowly	Frontal bone	Eburnated bony tumor, size of a large walnut	....	Removed
23 Kretschmann, 1910, quoted by Luxembourg	F	20	..	..	Bony hard tumor, apparently symptomless; history of chronic otitis media	Squamotemporo-occipital bone	Eburnated ivory-like bony tumor, 2.5×2.5 cm.	....	Removed
24 Kretschmann, 1910, quoted by Luxembourg	F	19	..	..	Bony hard tumor, size of pin-head at first, apparently symptomless	Mastoid bone	Fibrous tissue surface underlying cortical bone	....	Removed
25 Orator, 1931	F	22	10	12	Bony hard tumor, parietal bone since 10 years of age; second tumor arose in the outer surface of the orbit at 14 years; severe headaches and occasional dizziness for past few years; general physical and neurologic examinations gave negative results; Wassermann reaction negative; skin normal and freely movable	Right parietal bone and right frontal bone above orbit	Bony tumor size of male fist, weighing 470 Gm.; spongy type; inner surface of skull normal; showed markings of vessels	....	Removed; discharged well
26 Luxembourg, 1918	F	19	Birth	19	Bony hard tumor, symptomless; general physical and neurologic examinations negative	Temporoparietal region	Size of male fist; part of tumor ivory-like, especially at edges; central region of tumor spongy	Central spongy bone with abundant fibrous-osseous tissue; adult cortical bone at edges	Removed; discharged well

* Cases 1 to 7 are presented for the first time. Cases 8 to 26 are from the literature.

EFFECT OF MORPHINE ON OBSTRUCTED INTESTINE

ALTON OCHSNER, M.D.

I. M. GAGE, M.D.

AND

R. A. CUTTING, M.D.

NEW ORLEANS

Even earlier than 1500 B. C. opium was used in the treatment of diseases of the gastro-intestinal tract. In the Papyrus Ebers,[1] the following prescription was suggested "to clear out the body and to get rid of the excrement in the body of a person":

Leaves of the castor oil plant	¼
Dates of the male palm	⅝
Cyperus grass	1⁄16
Stalk of the poppy plant	1⁄16
Coreander	1⁄16
Cold beer	½

Keep moist, strain and take for four days.

At the present time morphine is undoubtedly one of the most valuable drugs which the surgeon has in his armamentarium, and without it or some of the other derivatives of opium, postoperative convalescence would be associated with prolonged and unnecessary suffering. Many surgeons, however, use morphine sparingly because of its supposed inhibiting effect on the intestinal motility and because of the fear of producing or increasing an already existing ileus.

Because of the constipating effect of morphine, which has been considered due to an inhibition of intestinal activity, the drug has been considered by most surgeons almost a specific in limiting the spread of peritoneal infection. In such cases and in those of contamination it has been used in large doses in order to "splint" the bowel. Perusal of some of the more recent textbooks on surgery[2]

1. Papyrus Ebers, translated from the German by C. P. Bryan, New York, D. Appleton and Company, 1931.
2. Ashhurst, A. P.: Surgery: Its Principles and Practice, ed. 4, Philadelphia, Lea & Febiger, 1931. Blake, J. A.: Peritonitis, in Diseases of the Peritoneum, Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1928, vol. 5. Stewart, F. T., and Lee, A. E.: Manual of Surgery, ed. 6, Philadelphia, P. Blakiston's Son & Co., 1931. Hartwell, J. A., and Cooper, H. S. F.: Intestinal Obstruction of the Ileus, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1930, vol. 7. Jones, D. F., and McClure, W. L.: The Peritoneum, ibid. Romanis, W. H. C., and Mitchiner, P. H.: Science and Practice of Surgery, ed. 2, New York, William Wood & Company, 1929, vol. 2.

shows that almost without exception the administration of morphine is suggested in cases of peritonitis because of the supposed inhibiting effect which the alkaloid exerts on the intestines.

The pharmacologic effects of opium and its derivatives, especially as regards their influence on intestinal activity, apparently vary in different species of animals. The majority of textbooks on pharmacology state that one of the chief actions of morphine on the intestinal tract is to decrease peristalsis (Cushney,[3] Solis-Cohen and Gilteus[4] and Wilcox[5]). Sollmann,[6] however, believes that the constipating effect of morphine is due to its action on the pylorus, i. e., spasmodic closure, which causes the food to enter the intestine more slowly than normally. In addition, he is of the opinion that morphine diminishes rectal sensation, which in turn decreases the sensitivity of the defecation reflex.

Considerable experimental work has been done on the effect of morphine on the normal intestine. As early as 1882, Nothnagel[7] found that small doses of morphine decreased intestinal activity whereas larger doses increased it. He believed that the action of the morphine was through the splanchnic nerves and that small doses of morphine stimulated, while large doses paralyzed, the splanchnics. Pal,[8] in 1900, found that opium and morphine invariably produced an increase in intestinal activity in dogs. He observed that the increase occurred even when the nerve supply to the intestine was cut, indicating that the action was on the peripheral ganglions. Magnus[9] showed by roentgenographic studies that the administration of morphine had little effect on the motility of the small intestine, but that by causing marked contraction of the pyloric antrum it produced constipation. Mahlo[10] found from roentgen examination of young persons receiving tincture of opium by mouth that there was considerable decrease in the motility of the small and large intestines. In

3. Cushney, A. R.: Textbook of Pharmacology and Therapeutics, ed. 6, Philadelphia, Lea & Febiger, 1915.

4. Solis-Cohen, S., and Gilteus, T. S.: Pharmacotherapeutics, New York, D. Appleton and Company, 1928.

5. Wilcox, R. W.: Materia Medica and Therapeutics, ed. 12, Philadelphia, P. Blakiston's Son & Co., 1929.

6. Sollmann, T.: Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926.

7. Nothnagel, H.: Ueber die Einwirkung des Morphins auf den Darm, Virchows Arch. f. path. Anat. **89**:1, 1882.

8. Pal, J.: Neue Untersuchungen über die Wirkung des Opiums und des Morphins auf den Darm, Wien. med. Presse **41**:2040, 1900.

9. Magnus, R.: Die stopfende Wirkung des Morphins, Arch. f. d. ges. Physiol. **115**:316, 1906; **122**:210, 1908.

10. Mahlo, Arthur: Ueber die Wirkung des Opiums auf den menschlichen Magen-Darmkanal, Deutsches Arch. f. klin. Med. **110**:562, 1913.

the same year, Schapiro,[11] also employing roentgenographic methods, found that the administration of morphine and other opium derivatives exerted little effect on the small intestine. He considered that the constipating effect of these substances was due to the diminished defecation reflex. Trendelenburg [12] found that the addition of morphine and other opium derivatives to perfusion fluids increased the activity of suspended loops of the intestines of dogs and cats but decreased the activity of the intestines of rabbits and guinea-pigs. Tsunemichi,[13] employing the same methods as Trendelenburg, found that if the suprarenal glands were removed or if splanchnicotomy was performed in rabbits, morphine exerted no inhibiting effect on the intestinal activity. Uhlmann and Abelin,[14] working with the isolated intestines of various animals, found that opium preparations in small doses always paralyzed, in large doses stimulated and in very large doses at first stimulated and later paralyzed, the intestine. Contrary to Trendelenburg's observations,[12] they found that the intestines of both rabbits and guinea-pigs, the latter less than the former, were stimulated by the administration of morphine. Plant and Miller,[15] working with Thiry fistulas in dogs, found that the injection of morphine caused marked increases in intestinal tone followed by increases in peristaltic movement. The increases in tone lasted from three to twelve hours. Because they obtained a typical reaction with loops of intestine which had been denervated, and after the administration of atropine, they expressed the belief that the action of morphine is peripheral and is exerted on the plexuses of Meissner and Auerbach. In addition to the experiments with animals, Plant and Miller [15] found that similar effects were obtained by the administration of morphine to human beings. King and Church,[16] working with Magnus' preparations of intestinal musculature, found that the administration of morphine was without effect either on the tone or on the rhythm of the muscle unless large doses were given, which acted as a depressant. Miller and

11. Schapiro, N.: Ueber die Wirkung von Morphium, Opium und Pantopon auf die Bewegungen des Magen-Darm-Tractus des Menschen und des Tieres, Arch. f. d. ges. Physiol. **151**:65, 1913.

12. Trendelenburg, P.: Physiologische und pharmakologische Versuche über die Dünndarmperistaltik, Arch. f. exper. Path. u. Pharmakol. **81**:55, 1917.

13. Tsunemichi, Hayama: The Rôle of the Suprarenals in the Sedative Effect of Morphine on the Intestine, Folia pharmacol. japon. F:10, 1928.

14. Uhlmann, F., and Abelin: Opium, Ztschr. f. exper. Path. u. Therap. **21**:58, 1920.

15. Plant, O. H., and Miller, G. H.: Effects of Morphine and Other Opium Alkaloids on Muscular Activity of Alimentary Canal: Action on Small Intestines in Unanaesthetized Dogs and Man, J. Pharmacol. & Exper. Therap. **27**:361, 1926.

16. King, C. E., and Church, J. G.: The Motor Reaction of the Muscularis Mucosae to Some Drugs, Am. J. Physiol. **66**:428, 1923.

Plant [17] found that even if morphine was given over long periods, tolerance of the intestine for the drug did not develop. Gruber, Crawford, Greene and Drayer [18] found that an antagonism exists between morphine and phenobarbital sodium, and between morphine and pituitary. The loss of tone produced by the administration of phenobarbital sodium could be combated by the administration of morphine. Following the administration of pituitary, morphine caused an increase in intestinal activity. The effects of morphine on the tone of the colon in both animals and human beings were determined by Plant and Miller.[19] Recording balloons were introduced into the lumen of the colon through fistulas. In all instances, the injection of morphine caused an increase in intestinal tone and movement. This stimulation occurred at times several hours after the injection of morphine. There was a return to normal in about eight hours. These authors expressed the belief that one of the constipating effects of morphine is due to the fact that because of the increased tone in the colon food is retained therein for longer periods, so that water is absorbed, making the stool less bulky. Similar results were obtained by Gruber and Robinson,[20] who found that the first injection of morphine always caused increases in tone and in amplitude of the intestine, whereas repeated injections tended to cause decreases in tone and in rhythmic contraction. Gruber, Greene, Drayer and Crawford [21] found that morphine and atropine acted antagonistically on intestinal musculature. The decrease in intestinal tone produced by the injection of atropine was combated by subsequent injections of morphine, whereas the injection of atropine at the height of an increased intestinal activity produced by morphine caused a marked drop in tone, the loss usually being recovered slightly.

17. Miller, G. H., and Plant, O. H.: Effect of Morphine and Other Opium Alkaloids on Muscular Activity of Alimentary Canal: Influence of Continued Administration of Morphine and of Withdrawal on Contractions of Small Intestines of Dogs, J. Pharmacol. & Exper. Therap. **28**:241, 1926.

18. Gruber, C. M.; Crawford, W. M.; Greene, W. W., and Drayer, C. S.: The Effect of Sodium Phenobarbital and the Antagonism of Morphine to Phenobarbital and to Pituitary Extract in Intact Intestine in Non-Anaesthetized Dogs, Proc. Soc. Exper. Biol. & Med. **42**:27, 1927.

19. Plant, O. H., and Miller, G. H.: The Effect of Morphine and Some of the Other Opium Alkaloids on the Muscular Activity of the Alimentary Canal: IV. Action of Morphine on the Colon of Anaesthetized Dogs and Man, J. Pharmacol. & Exper. Therap. **32**:437, 1928.

20. Gruber, C. M., and Robinson, P. I.: Intestinal Activity in Unanaesthetized Dogs as Influenced by Morphine and Papaverine, J. Pharmacol. & Exper. Therap. **37**:101, 1929.

21. Gruber, C. M.; Greene, W. W.; Drayer, C. S., and Crawford, W. M.: Further Studies on the Effect of Morphine Sulphate, Atropine Sulphate, and Hyoscine Hydrobromide upon the Intact Intestine in Unanaesthetized Dogs, J. Pharmacol. & Exper. Therap. **38**:389, 1930.

Gruber and Pitkin,[22] working with Thiry fistulas and isolated segments of intestine, found that morphine invariably increased the activity. Dvorak, Carlson, Erickson, Smith and Wangensteen,[23] in experimental and clinical observations, found that injections of morphine produced in the normal bowel of both human beings and dogs immediate increases in intestinal tone followed by increases in peristaltic activity. These were more marked in the small than in the large bowel. In intestinal obstruction, a similar response to the administration of morphine was observed. In five patients and ten animals with intestinal obstruction there were evidences of increased activity as determined by increased peristaltic sounds. Gruber, Bryan and Richardson[24] found that morphine, when injected intravenously, given by mouth or inserted into the lumen of the intestine through a Thiry fistula, caused an increase in intestinal tone and temporary cessation of peristalsis in animals. Wilen and Dragstedt[25] found that in the presence of peritonitis injections of morphine caused an increase in intestinal movement.

<div align="center">EXPERIMENTS</div>

Because of the widespread use of morphine in surgical practice, and because most of the recent studies have been made on normal and not on obstructed intestines, the present investigation was undertaken. Dogs were chosen as the experimental animals. Twenty-three observations concerning the effect of morphine on obstructed intestines were made in eighteen dogs. In three additional animals, three observations were made of the effect of a mixture of the hydrochlorides of the opium alkaloids on obstructed intestines. Four observations were made on animals with obstruction of forty-eight hours' duration and nineteen on animals with obstruction of seventy-two hours' duration. The three observations in which the mixture of the hydrochlorides of the opium alkaloids was used were made on animals with obstruction of seventy-two hours' duration. The obstruction was produced as follows:

With the animal under ether anesthesia, and with aseptic technic, a laparotomy was performed. The terminal ileum was obstructed by tying binding tape tightly

22. Gruber, C. M., and Pitkin, Garrett: Further Observations on the Effect of Pituitary Extract and Morphine Sulphate upon Excised Dogs' Intestines, J. Pharmacol. & Exper. Therap. 38:401, 1930.

23. Dvorak, H. J.; Carlson, H. A.; Erickson, T. C.; Smith, V. D., and Wangensteen, O. H.: Influence of Morphine on Intestinal Activity in Experimental Obstruction, Proc. Soc. Exper. Biol. & Med. 28:434, 1931.

24. Gruber, C. M.; Bryan, W. T., and Richardson, L. R.: Response of Intact Small Intestine in Non-Anaesthetized Dogs to Cathartic Agents, to Morphine and Atropine, Proc. Soc. Exper. Biol. & Med. 28:470, 1931.

25. Wilen, C. J., and Dragstedt, C. A.: Action of Morphine on Intestine in Peritonitis, Proc. Soc. Exper. Biol. & Med. 28:1056, 1931.

around the terminal portion of the ileum. Care was taken not to tie the tape so tightly that necrosis would result. After varying periods, from twenty-four to seventy-two hours, the animal was again operated on. Two tubes were introduced into the dilated obstructed intestine proximal to the obstruction; one served as an enterostomy tube, and the other, which was introduced proximal to the enterostomy tube, carried a rubber balloon. The second, or recording, tube was connected with a tambour so that kymographic tracings of the activity of the bowel could be recorded. The animal was placed in a bath of salt solution, as described in previous publications,[26] and kymographic tracings were made.

<div style="text-align:center">OBSERVATIONS</div>

Four observations were made on three animals with obstructions of forty-eight hours' duration. In two experiments, ⅛ grain (7.5 mg.) of morphine was injected subcutaneously; in the other two experiments, ¼ grain (15 mg.) was given. There was increased activity in three instances (75 per cent), and no change occurred in one (25 per cent). In the latter instance, however, the morphine was given at the height of an increase in activity caused by a previous injection of morphine, and therefore one probably should consider that there was no change. The average increase in tone was 83.3+ mm. (fig. 1). The average increase in amplitude was 28.3 mm., and the average duration of the activity was thirty-two and six tenths minutes (fig. 2). The activity persisted longer than these figures would indicate, because in two instances the intestine was still active at the termination of the experiment. The average dose was 2.6 mg. per kilogram of body weight. There was no change in blood pressure.

Nineteen observations were made in fifteen dogs with obstructions of seventy-two hours' duration. Five of these could not be used because the intra-intestinal balloon leaked. In one of the fourteen observations that were used, the balloon was leaking. In another, the morphine was given after the administration of 10 per cent dextrose solution, which we[27] have shown to exert an inhibiting effect on the intestine. In thirteen (92.8 per cent) there were increases in intestinal activity, and in one (7.2 per cent) there was no change. The average increase in tone in the experiments in which there was normal activity was 43.1 mm. (figs. 3 and 4). In one instance, the increase was much greater than this, as the lever passed off the kymographic drum. The average increase in amplitude was 13 mm. (fig. 5). The average duration of the increased activity was twenty-eight and three tenths minutes plus. That the duration was much longer is proved by the

26. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: Comparative Value of Splanchnic and Spinal Analgesia in the Treatment of Experimental Ileus, Arch. Surg. **20**:802 (May) 1930.

27. Gage, I. M.; Ochsner, Alton, and Cutting, R. A.: Effect of Insulin and Glucose on Normal and Obstructed Intestine, Proc. Soc. Exper. Biol. & Med. **29**:264, 1931.
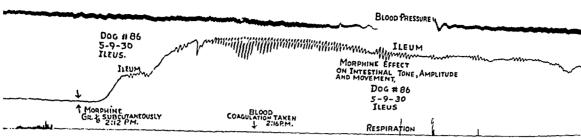
Fig. 1.—Kymographic tracing showing the stimulating effect of morphine (⅛ grain [7.5 mg.] injected subcutaneously) on an intestine obstructed for forty-eight hours. As indicated by the arrow on the left side, the morphine was injected at a time when the bowel was motionless. Within thirty seconds there was a rapid rise in tone, which was followed by increased movement. The increased tone persisted.

Fig. 2.—Kymographic tracing showing the effect of morphine (¼ grain [15 mg.]) on the activity of an intestine obstructed for forty-eight hours. The arrow at the left of the tracing indicates the injection of morphine. Within one minute after the injection there was a marked rise in tone, associated with a definite increase of movement. The rise in tone was so great that the writing lever struck against the clock lever. The action was prolonged.
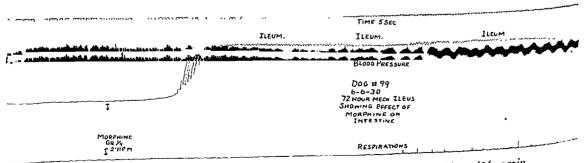
Fig. 3.—Kymographic tracing showing the effect of morphine (¼ grain [15 mg.]) on the activity of an intestine obstructed for seventy-two hours. The arrow at the left of the tracing indicates the injection of morphine. Within approximately a minute and a half after the injection there was a sudden increase in tone, which was associated with only a slight increase in amplitude. The increased tone persisted.
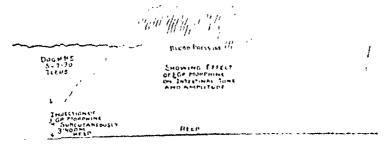
Fig. 4.—Kymographic tracing showing the effect of morphine (¼ grain
[15 mg.]) on the activity of an intestine obstructed for seventy-two hours. The
arrow at the left of the tracing indicates the injection of morphine. Within one
minute after the injection there was a sudden rise in tone, which reached its
maximum after approximately two minutes and was then associated with a marked
increase in movement. After four minutes the tone fell somewhat; it reached a
higher level than before the injection of morphine and persisted at this level.
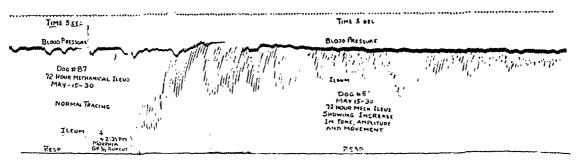
Fig. 5.—Kymographic tracing showing the effect of morphine (¼ grain
[15 mg.]) on the activity of an intestine obstructed for seventy-two hours. The
arrow at the left of the tracing indicates the injection of morphine. Within one
minute after the injection there was a marked increase in intestinal movement with
a rise in intestinal tone, which persisted until the end of the experiment.
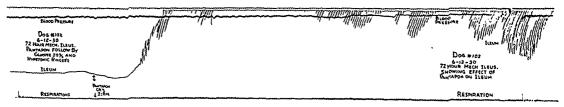
Fig. 6.—Kymographic tracing showing the effect of subcutaneous injection of
a mixture of opium alkaloid hydrochloride (⅓ grain [20 mg.]) on the activity
of an intestine obstructed for seventy-two hours. The arrow at the extreme left
of the tracing indicates the injection of the preparation. Within two minutes after
the injection there was a sudden rise in tone with an increase in movement. The
bowel became tonically contracted, but later the tonic spasm was replaced by
periods of increased intestinal movement.

fact that in six of the thirteen observations in which there was increased activity, the intestine was still active at the termination of the observation. The average dose of morphine used was 1.8 mg. per kilogram of body weight. There was no change in the blood pressure except in two observations in which there was a gradual fall. In three animals with obstructions of seventy-two hours' duration, observations were made of the effect of the administration of a mixture of the hydrochlorides of opium alkaloids. In each instance, ⅓ grain (20 mg.) was administered. There was an average increase of tone of 36.6 mm., with an average increase in amplitude of 14.6 mm., and the average duration of the increased activity was twenty-two minutes (fig. 6). In two of these animals, however, dextrose solution was given at the height of activity, which undoubtedly influenced the effect of the mixture of the hydrochlorides of the opium alkaloids. The average dose of the opium alkaloid preparation used was 2.4 mg. per kilogram of body weight.

COMMENT

From these experimental observations and from those of others, both experimental and clinical, it is apparent that the present conception of most clinicians, especially surgeons, that morphine and other opium derivatives exert an inhibiting action on the intestine is incorrect. That morphine is constipating is well known and cannot be denied. The constipating effect of opium derivatives is undoubtedly responsible for the erroneous conception that these substances inhibit intestinal activity, whereas, as suggested by Sollmann,[6] the constipating effect is probably due to spasmodic closure of the pylorus and diminished rectal sensitivity. It is possible, as suggested by Plant and Miller,[19] that dehydration of the intra-intestinal contents may be a factor. Plant and Miller [19] expressed the belief that, as a result of the increased intestinal tone, food may remain in the intestine for longer periods, which permits extraction of water.

Most surgeons, even though they realize the value of the postoperative use of morphine, feel that it should be employed cautiously, because of the danger of inhibiting intestinal peristalsis. We are convinced from our own clinical experience that morphine in no way favors ileus. On the contrary, its administration has been beneficial in cases of ileus. Previously we felt that the analgesic properties of morphine were responsible for the improvement noted in patients with ileus, but we now realize that the stimulating action is also important. In the present investigation all observations were made on obstructed intestines. The beneficial results obtained from the administration of opiates in cases of peritonitis are not due to the "splinting" of the bowel, but are probably due to the analgesic and sedative properties

of the drugs. Even though morphine not only does not inhibit intestinal movement but actually increases it, it is probable that in the presence of intense peritoneal irritation, such as is caused by peritonitis, morphine exerts little or no stimulating effect. This probably explains why opiates are not harmful in peritonitis.

The efficacy of morphine as a stimulant of intestinal movement is demonstrated by comparing results obtained in experimental ileus by the administration of morphine and of hypertonic salt solutions. The latter, since the original observations of Hughson and Scarff [28] and Ross,[29] have been known to exert a powerful stimulating effect on the motility of the intestine. We [30] have demonstrated, both clinically and experimentally, that hypertonic Ringer's solution intravenously administered is more efficacious in stimulating intestinal activity than hypertonic solutions of sodium chloride. Whereas the administration of morphine to animals with intestinal obstruction of forty-eight hours' duration caused average increases in tone and amplitude of 83 mm. and 28 mm., respectively, the intravenous administration of hypertonic Ringer's solution caused average increases in tone and amplitude of 62 and 11 mm., respectively. The average duration of the increased activity in the experiments with morphine was thirty-two minutes, and in those with Ringer's solution, twelve and four-tenths minutes. The results obtained in the two investigations are not entirely comparable because of the difference in the number of observations, four being made with morphine and fourteen with Ringer's solution. The administration of morphine to animals with obstruction of seventy-two hours' duration caused average increases in intestinal tone and amplitude of 43 and 13 mm., respectively, whereas in similar experiments the intravenous injection of hypertonic Ringer's solution caused average increases in tone and amplitude of 64 and 18 mm., respectively. The average duration of the increased activity in the experiments with morphine was twenty-eight minutes, and in those with Ringer's solution, twenty minutes.

It is evident that morphine is a definite stimulant to intestinal activity, and that it can even be compared with hypertonic salt solution in its efficacy, although on intestines obstructed for seventy-two hours, its effect was less marked than that of the salt solution.

28. Hughson, W., and Scarff, J. E.: Influence of Intravenous Sodium Chloride on Intestinal Absorption and Peristalsis, Bull. Johns Hopkins Hosp. 35:197, 1924.

29. Ross, J. W.: Hypertonic Saline in Adynamic Ileus, Canad. M. A. J. 16: 241, 1926.

30. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: Treatment of Experimental Ileus by Hypertonic Saline Solutions, Proc. Soc. Exper. Biol. & Med. 29:911, 1932; Influence of Hypertonic Salt Solution on the Motility of Normal and Obstructed Intestine: An Experimental Study, Arch. Surg., to be published.

CONCLUSIONS

1. Contrary to the opinions of most clinicians, opium derivatives stimulate rather than inhibit the activity of the small intestine.

2. The present investigation demonstrates that the administration of morphine and of a mixture of the hydrochlorides of the opium alkaloids to animals with intestinal obstruction greatly increases the activity of the intestine.

FIFTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

JOHN G. KUHNS, M.D.

EDWIN F. CAVE, M.D.

SUMNER M. ROBERTS, M.D.

AND

JOSEPH S. BARR, M.D.

BOSTON

JOSEPH A. FREIBERG, M.D.

CINCINNATI

JOSEPH E. MILGRAM, M.D.

NEW YORK

ROBERT I. STIRLING, M.D.

EDINBURGH, SCOTLAND

AND

PHILIP D. WILSON, M.D.

Advisory Editor

BOSTON

CONGENITAL DEFORMITIES

Early Treatment of Congenital Dislocation of the Hip.—Putti[1] reviewed 119 cases of congenital predislocation of the hip. Complete cure has been obtained in 113. The author advocated routine roentgen examination of the hips of infants in order that the condition might be recognized early and treatment begun immediately by the abduction method.[2] This method was applicable to all children under 12 months of age.

ENDOCRINE REGULATION OF CALCIUM METABOLISM

Rôle of Parathyroid Glands in Diseases Associated with Demineralization of the Human Skeleton.—Compere,[3] from his observations in cases of generalized osteitis fibrosa, Paget's disease and polyarthritis,

1. Putti, V.: J. Bone & Joint Surg. **15**:16, 1933.
2. Putti, V.: J. Bone & Joint Surg. **11**:838, 1929.
3. Compere, E. L.: J. Bone & Joint Surg. **15**:142, 1933.

concluded that the first condition was always associated with an adenomatous tumor of the parathyroid gland and was characterized by a high serum calcium content, low plasma phosphates, increased excretion of calcium in the urine and a negative calcium balance. He stated that there was no good evidence that Paget's disease was caused by hyperparathyroidism; that ankylosing polyarthritis was not caused by hyperparathyroidism, and that the atrophy of the skeleton in polyarthritis was due to disuse.

Regulation of Blood Calcium Level Through Parathyroid Hormone.—Spiegler and Stern[4] reported their observations on the use of parathyroid hormone in rabbits, in normal persons and during pregnancy. After injection of parathyroid hormone, there was a rise in the calcium level which was most marked in the experimental animals. The rise in the blood calcium took the form of a curve with its maximum in from one to two hours. No relationship could be found between the decline of the curve and the amount of hormone given. The rise of the blood calcium was not considered by the author to be a specific action of the hormone since a rise could be produced by other substances such as prolan or epinephrine. Changes in galvanic excitability did not run parallel with the amount of blood calcium. The authors were led to conclude that the parathyroid hormone in both normal and pathologic states acted as a regulator in attempting to maintain the serum calcium at a normal level.

OSTEOMYELITIS

Early Diagnosis of Acute Osteomyelitis of the Spine.—Esau[5] called attention to the presence of edema and purulent collections in vertebral osteomyelitis as shown in roentgenograms. Shadows similar to those seen in tuberculous spondylitis were shown in illustrations in 2 cases. In both of these pus was obtained on incision, and the shadows disappeared on recovery. In one case the lower dorsal vertebrae were involved; in the other, the low lumbar vertebrae.

Acute Osteomyelitis of the Vertebrae.—Klein[6] studied 18 cases of acute osteomyelitis of the vertebrae; 16 of these he reported in detail. All were metastatic from boils, previous chronic osteomyelitis, pneumonia, cellulitis and phlebitis. He divided his patients into four groups: (1) those showing abscess formation anywhere along the spine; (2) those presenting complaints referable to the nervous system due to involvement of nerve roots; (3) those presenting only pain in the back and fever, and (4) those suffering from widespread bac-

4. Spiegler, R., and Stern, K.: Ztschr. f. Geburtsh. u. Gynäk. **104**:250, 1933.

5. Esau, P.: Deutsche Ztschr. f. Chir. **239**:615, 1933.

6. Klein, H. M.: Acute Osteomyelitis of the Vertebrae, Arch. Surg. **26**:169 (Feb.) 1933.

teremia and multiple abscesses. In 10 patients the processes of the vertebrae were involved. The roentgenograms were frequently negative. Treatment was always surgical, i. e., drainage of the osseous focus.

Osteomyelitis of the Scapula.—Giubal and Montagne [7] made a systematic study of the various types of osteomyelitis of the scapula. How much their study was based on actual cases is hard to determine, although some case histories were given. They found that osteomyelitis of the scapula occurred as a rule in the second decade of life, that it was twice as common in males as in females, and that the pathogenic organism in all cases was Staphylococcus aureus which gained entrance in most cases through the skin. The different types of osteomyelitis were classified according to the location: (1) supraspinous; (2) infraspinous; (3) subscapular; (4) articular; (5) axillary, and (6) diffuse periscapular. Diagnosis, treatment and complications were discussed under each of the six headings.

Peculiarities of Osteomyelitis in Early Childhood.—Paschlau [8] studied the peculiarities of osteomyelitis in early childhood at the Children's Hospital of Berlin. In 42 cases of osteomyelitis of the long bones in infants, diaphyseal localization was observed only 5 times. Almost always the disease was found in the metaphysis. Often purulent arthritis in the nearby joints occurred, particularly when the epiphysis was for the most part intra-articular, by spreading along the epiphysis, but not through the cartilage. The bones most frequently affected were the femur, humerus and tibia. The proximal ends were most commonly involved. The short bones and flat bones were involved frequently in infants, with decreasing frequency with each year of age. Suppurative arthritis was the commonest complication and was observed in 41 per cent of the cases seen in infants. Separation of the epiphysis was the next most common complication, occurring in 20 per cent of the infants. Bowing at the metaphysis was not infrequently seen. Secondary foci of osteomyelitis were not necessarily of grave prognosis; of 7 infants with two foci, 4 recovered. It was not the number of septic metastases but their localization which modified the prognosis. The least serious localizations were in bones, muscles and joints. Of the 13 fatal cases, 9 were cases of extensive osteomyelitis with metastases to vital organs. In these, abscess of the lung occurred 3 times, generalized pyogenic abscesses 4 times, and pneumonia, mastoiditis and meningitis, once. In the other 4 cases metastases occurred late; in one case, endocarditis, and in another, pericarditis, with a progressive decrease in resistance. The formation of sinuses and sequestrums were uncommon, but metastases to joints and other tissues were the characteristics

7. Giubal, A., and Montagne, J.: Rev. de chir. **52**:268, 1933.
8. Paschlau, G.: Monatschr. f. Kinderh. **55**:280, 1933.

of osteomyelitis of infancy. One case of osteomyelitis of the vertebra in a 21 month old infant was observed. Bacteriologic investigations were not recorded. The operative procedure was usually limited to opening the abscess at the metaphysis without disturbing the bone. Further high temperature was usually due to metastases to the joint or to other tissues.

POLIOMYELITIS

Prevention of Poliomyelitis.—In a résumé of the investigation of the immunologic phenomena in poliomyelitis, Flexner [9] concluded that whether or not it could be definitely proved that convalescent serum therapy was of benefit, the patient should be given the serum, as the choice lay between no therapy and a kind of intervention believed to be harmless and perhaps sometimes useful in this disease. The advantage of passive serum protection during epidemics seemed to have been proved in part, and the possible future of active immunization was considered.

CHRONIC ARTHRITIS

Surgical Treatment of Osteo-Arthritis of the Hip.—Operative treatment was considered by Groves [10] to be specially indicated in mono-articular osteo-arthritis of comparatively young patients and in those cases in which trauma has been a causative factor and pain a prominent result. Different operative procedures were suggested to meet various requirements; cheilotomy, in cases of marked osteophytic outgrowths resulting from trauma and confined to one hip; arthroplasty, by reducing the head or removing the inferior part of the acetabulum, for hips with deep sockets when the head and neck were enlarged so that the joint became "seized"; arthrodesis, in single painful hips; excision, on the worst side in cases of bilateral stiff and painful hips, and osteotomy, in cases of coxa vara or subluxation.

Cystic Nodules of Terminal Finger Joints.—Nachlas [11] reported a study of cystic nodules of the terminal phalanges of the finger joints. He removed and studied 28 specimens from 25 cases and treated another group symptomatically. He concluded that the gelatinous filled cysts represented a preosseous stage of Heberden's nodes. They showed a high calcium content but no uric acid or urates. He recommended removal of the cysts under local anesthesia (ethyl chloride) for cosmetic reasons.

Roentgenotherapy in Arthritis.—Langer [12] advocated high voltage roentgenotherapy as an important aid in the treatment of atrophic arthri-

9. Flexner, S.: Brit. M. J. **1**:132, 1933.

10. Groves, E. W.: Brit. M. J. **1**:3, 1933.

11. Nachlas, I. W.: Cystic Nodules of Terminal Finger Joints, Arch. Surg. **25**:1067 (Feb.) 1932.

12. Langer, H.: Radiology **20**:78, 1933.

tis. In addition to treating involved joints directly, he also gave paravertebral treatments in order to influence the sympathetic ganglions supplying the affected areas. The rationale of this procedure was based on the opinion that the x-rays have some effect on the vegetative nervous system which produced better circulation and tissue metabolism. Beneficial results were observed in patients who did not receive any other sort of treatment. Langer advocated the use of the x-rays before attempting any surgical measures on the sympathetic ganglions. In addition to their effect on the sympathetic nervous system, the x-rays lessened anaphylactic reaction, had a direct effect on lymphocytes and leukocytes, reduced general inflammation and pressure on nerve sheaths and had an analgesic effect. The technic and dosage were described.

[ED. NOTE.—The place of roentgenotherapy in the treatment of arthritis is still in question. We advise caution in its use until more definite knowledge of its effect on diseased joints is obtained.]

NEOPLASMS

Chondroma of the Intervertebral Disk.—Alpers, Grant and Yaskin [13] reported a single case of "chondroma" of the intervertebral disk in a woman. Symptoms came on after a severe fall on the coccyx and were relieved completely by operative removal of the tumor. They found 35 such cases in the literature: of these, 46 per cent involved the cervical area; 37 per cent the lumbar region, and 17 per cent the thoracic region. The authors felt that these tumors developed as an outgrowth of the fibro-cartilaginous annulus fibrosus rather than from the nucleus pulposus since they were comprised chiefly of fibrocartilage. A worthwhile review of the entire subject and of the current literature was given.

Early Diagnosis of Malignant Disease of the Bone.—The complexity of early accurate diagnosis of osteogenic sarcoma, of either the osteoplastic or the osteolytic variety, was emphasized by Brockman,[14] who took the salient points to be: pain, which was more severe if the periosteum remained intact; rapidity of growth; tactile sensation, and roentgenographic examination. The importance of excluding gummatous osteitis was mentioned, but biopsy in such cases was condemned. In doubtful cases roentgenotherapy was advised, not as a curative, but as a diagnostic, measure, since under its influence, for a time at least, sarcomas, as opposed to inflammatory conditions, showed an increase of bone formation. Primary malignant disease of the spine was rare, and although secondary malignant deposits were common, if the primary focus in these cases was unknown, the diagnosis might be somewhat difficult. Secondary growths from a hypernephroma were most commonly found

13. Alpers, B. J.; Grant, F. C., and Yaskin, J. C.: Ann. Surg. **97**:10, 1933.
14. Brockman, E. P.: Practitioner **130**:199, 1933.

in the greater trochanter and bones of the pelvis, and usually exhibited a marked pulsation which in some cases facilitated the differentiation from secondary carcinomatous deposits.

THE BACK

Lumbar and Lumbosacral Diarthrodial Joints.—From the examination of 44 skeletons, Odgers [15] concluded that the hypersthenic form of articular facets in the lumbar region was more common in females, and the asthenic in males. This was true to a less marked extent in the lumbosacral joints. The superior articular processes began to open at the third lumbar vertebra, and in the vertebrae below this level the tendency of the articular surfaces was to increase in inclination toward the frontal plane. The difference in degree of inclination of the articular facets was due, he suggested, to variations in development and to the activity of the multifidus spinae muscle.

Accessory Articular Process of the Lumbar Vertebra.—Rendich and Westing [16] observed "accessory articular processes" in 5 patients. Two cases of this anomaly had been reported in the German literature. There was a separate ossicle occurring at the lower end of the articular process of the second and third lumbar vertebrae. It was distinguishable from fracture by the absence of a history of trauma and by the roentgenologic appearance. In one case the variation was bilateral.

Significance and Treatment of Sciatic Pain.—Craig and Ghormley [17] summarized the various causes for sciatic pain and then discussed the treatment in those cases in which no known cause could be found. One group of patients was treated in the hospital and another group given ambulatory treatment. In the first group the results of rest, diathermy, Buck's extension, intravenous injection of foreign protein and elimination of foci of infection with and without epidural injections were considered. For the second group the results of epidural injections, sacro-iliac belts and diathermy alone and in various combinations were studied. A fairly high percentage of patients receiving institutional care were completely relieved of their symptoms. Fewer ambulatory patients were relieved but enough to make this sort of treatment worth while when hospitalization was not feasible.

SURGERY OF THE BONES AND JOINTS

Operative Treatment of the Ankylosed Joint.—Campbell [18] reviewed an extensive experience (325 cases) with arthroplasty of various types

15. Odgers, P. N. B.: J. Anat. **67**:301, 1933.
16. Rendich, R. A., and Westing, S. W.: Am. J. Roentgenol. **29**:156, 1933.
17. Craig, W., and Ghormley, R.: Significance and Treatment of Sciatic Pains, J. A. M. A. **100**:1143 (April 15) 1933.
18. Campbell, W. C.: Surg., Gynec. & Obst. **55**:747, 1932.

and regions. He considered in detail the indications and contraindications, operative technic, postoperative care, complications and end-results. The paper gave a concise summary of the present state of knowledge concerning this type of procedure. The article should be read in detail.

Operative Arrest of Longitudinal Growths.—At the University of Chicago Clinic 34 patients were operated on for arrest of growth of an extremity because of inequality in length. The operation consisted of "epiphyseo-diaphyseal fusion." The technic of this procedure was described by Phemister.[19] Among the common conditions resulting in inequality of length of extremities were: (1) fractures involving the epiphysis; (2) infection of the joints with epiphyseal destruction; (3) infections of the bones; (4) tumors of the bone; (5) congenital disturbances and (6) infantile paralysis.

Operative Fixation of Tuberculous Hips in Children.—Wilson[20] made a preliminary report of a study of 33 patients on whom 38 operations were performed to secure ankylosis in tuberculosis of the hip. The operation called "iliofemoroplasty" consisted in turning down from the ilium a wide flap of bone into a slot between the trochanter and the femoral neck. Wilson advocated the operation at any age, since he felt that it did not interfere with growth. Fusion was not done in any case until the diagnosis was established by either biopsy or inoculation into guinea-pigs. Twenty-seven of 33 patients obtained ankylosis as shown both clinically and by roentgenograms. The position of fixation was from 15 to 20 degrees flexion and 10 degrees abduction.

Combined Intra-Articular and Extra-Articular Arthrodesis for Tuberculosis of the Hip Joint.—Henderson[21] reported the end-results in 35 cases of tuberculous hips in which fusion was employed. The ages of the patients ranged from 9 to 48 years. Twenty-seven, or 73 per cent, were between the ages of 10 and 30 years. Operation was performed in 34 cases in the chronic stage of the disease; the thirty-fifth case was in the subacute stage. In 19 patients a combination of the intra-articular and extra-articular methods with a bone graft was used. In 16 cases fusion was attempted by extra-articular methods. Bony union was obtained in 91.4 per cent; the average time before bony union was secured was eight and four-fifths months. Henderson felt that a combination of the intra-articular and extra-articular methods with bone graft was the most effective procedure.

Operative Treatment of Paralytic Genu Recurvatum.—Campbell and Mitchell[22] devised a new operation for the treatment of genu recurvatum

19. Phemister, D. B.: J. Bone & Joint Surg. **15**:1, 1933.
20. Wilson, J. C.: J. Bone & Joint Surg. **15**:22, 1933.
21. Henderson, M. S.: J. Bone & Joint Surg. **15**:51, 1933.
22. Campbell, W. C., and Mitchell, J. I.: Ann. Surg. **96**:1055, 1932.

resulting from infantile paralysis. The operation consisted in fusing the inferior portion of the patella to the anterior aspect of the head of the tibia so that the knee was blocked in complete extension or in a few degrees of hyperextension. Seven patients had been operated on with satisfactory results. In 1, the operation was performed on both knees. The authors felt that the results obtained were superior to those following supracondylar osteotomy of the femur and thought that the effect was more permanent than that secured by any form of ligamentous fixation.

[ED. NOTE.—The effect of bone block operations on the knee has not been sufficiently tested to allow definite conclusions to be drawn. There may be danger of traumatic arthritis developing later and also the possibility of recurrence of the deformity due to strain on the graft.]

Extensive Loss of Tibial Diaphysis; Tibiofibular Grafting.— Girdlestone and Foley [23] described a case with extensive loss of the tibial diaphysis through osteomyelitis. Treatment consisted of buttressing the fibula, which was left in its normal position, against the remaining proximal and distal portions of the tibia. From the other tibia one long and two short osseous grafts and one large osteoperiosteal graft were taken. The long graft was laid on the exposed fibular ends within the raised periosteum; the two short grafts were implanted into the tibial ends and bridged over to the fibula; the osteoperiosteal graft was placed over all, thereby completing the periosteal sheath. Plaster fixation for five months was followed by the use of a modified Delbert's walking plaster. Two years later there was no shortening, and the patient was leading a normal life.

*Stump Lengthening Through Transplantation of Bone.—*Kraus [24] reported the lengthening of a functionally useless humeral stump in a patient with a humerus which was only 13 cm. long with muscles which extended 6 cm. farther distally. The author lengthened the stump 5 cm. by driving a portion of one fibula into the reamed-out marrow cavity of the humerus. The functional result was excellent.

23. Girdlestone, G. R., and Foley, W. B.: Brit. J. Surg. **20**:467, 1933.
24. Kraus, H.: Deutsche Ztschr. f. Chir. **240**:237, 1933.

(To be Concluded)

MECKEL'S DIVERTICULUM CONTAINING ABERRANT PANCREAS

VERNE C. HUNT, M.D.

AND

H. T. S. BONESTEEL, M.D.

LOS ANGELES

The condition of aberrant or accessory pancreas was first described by Klob in 1859. In 1860 Montgomery cited a case which was recorded by Bristowe in his book of necropsies in 1851, in which a pancreatic nodule ¾ in. (1.9 cm.) in diameter and ⅓ in. (0.83 cm.) thick was found in the wall of the ileum. The nodule was in the middle of the ileum and was lobulated in appearance. As early as 1727 Jean Schultz reported a case which, although it is not authentic, as there is no proof that the nodule found was pancreatic, is interesting from a historical standpoint. He wrote that he found at autopsy in a new-born child "a wart similar to a gland" in the apex of a cone-shaped diverticulum of the ileum. The diverticulum was 4 cm. long and was situated 10 cm. from the ileocecal valve.

Aberrant or accessory pancreas is an infrequent anomaly. Opie found 10 cases in 1,800 autopsies, and Horgan found 2 cases in 314 autopsies. Since Klob reported his case there have been approximately 186 instances of aberrant or accessory pancreas recorded. Warthin, in 1904, analyzed 47 previously reported cases and added 2 of his own. Horgan, in 1921, gathered together 32 additional cases from the literature and added 2 of his own, bringing the total of reported instances to 83. The last complete survey of the literature was made by Simpson in 1927. He collected 66 additional cases from the literature and added 1 of his own, making a total of 150 cases of accessory pancreas recorded in the literature. In the course of a review of the literature we found 36 additional cases recorded. Among these were 6 cases of pancreatic tissue in a diverticulum of the ileum, which had been reported earlier than 1927 but were not included by Simpson in his survey—1 of pancreatic tissue in a Meckel's diverticulum which Kaufmann mentioned having seen in the Baseler Museum, another of pancreatic tissue in Meckel's diverticulum, reported in 1928 by Schaetz, and 4 reported in 1904 by Schmauser and Heller and referred to by Bize. Since Simpson's publication in 1927, 29 additional cases of aberrant pancreas have been reported, in which the diagnosis was corroborated by microscopic section. In only 1 of these was the aberrant pancreas located in a

Meckel's diverticulum. The literature, as we have been able to review it, contains the reports of approximately 186 cases of aberrant or accessory pancreas. In 33 cases the aberrant pancreas existed in a diverticulum of the stomach, duodenum, jejunum or ileum, and in only 13 of these was the diverticulum described as a true Meckel's diverticulum. Our case of Meckel's diverticulum containing an accessory pancreas, herein reported and added to the literature, we believe to be the fourteenth recorded case.

TABLE 1.—*Cases of Accessory Pancreas Recorded in the Literature Since Simpson's Review in 1927*

Name of Recorder	Stomach	Duodenum	Gallbladder	Jejunum	Ileum	Meckel's Diverticulum	Total
Alessandri		1					1
Barcaroli	1						1
Cafritz		1					1
Cave		1				1	2
Cogniauz	2	3	1	1			7
Cox	1						1
de Gaetani		1					1
Haas	1						1
Hilarowicz	1					1	2
Kaufmann *		1					1
Lordy				1			1
Moore				1		1	2
Schaetz *					4		4
Schmauser *		1					1
Semsroth		1					1
Ssokolow		1					1
Sussi	1						1
del Valle and Brachetto-Brian	1						1
Vandendorpe	1	1					2
Weeks and Steinke		1					1
Wigrsussi	2						2
Wohlwill	1						1
Total	12	13	1	3	4	3	36

* Not included in previous articles but recorded in the literature prior to 1927.

Zenker, in 1861, recorded the first case of a Meckel's diverticulum containing pancreatic tissue. Since that time cases have been reported by Schirmer, Albrecht, Merkel, Hedinger, Kaufmann, Clogg, Nazari, Albrecht and Arzt, Koch and Suzuki, Schaetz and Cogniauz.

Oppel and Horgan completely reviewed the comparative anatomy and embryology of the pancreas and found that the pancreas is present in every species of Vertebrata from the cyclostomes (the lowest order of fishes) through amphibians, reptiles, birds and mammals to man. The form varies from numerous small and widely scattered glands to the single large gland found in man, and each phase of the embryologic development in man represents in a general way the mature development in the lower Vertebrata.

The anlage of the pancreas usually consists of two separate epithelial buds from the duodenum. The smaller bud arises from the anterior portion of the foregut at the junction of the primitive bile duct and

forms a portion of the head and uncinate process. The larger bud arises from the dorsum of the gut and forms the rest of the head and the body of the gland. These buds grow independently for some time and later coalesce to form the adult pancreas. Occasionally they fuse on both sides of the duodenum and completely encircle it, giving rise to the anomaly known as ring or annular pancreas.

Many theories have been advanced to explain the genesis of an aberrant pancreas. Zenker believed that it is due to an additional bud from the foregut which has developed into a single independent glandular mass, which, as the gut elongates, may be carried a great distance from its point of origin. Glinski believed that it is due to a failure of a primitive anlage to coalesce with the main pancreas. Warthin stated: "It is more probable that accessory pancreatic tissue is formed from lateral budding of the rudimentary pancreatic ducts as they penetrate the intestinal wall, the mass of pancreatic tissue thus formed being snared off and carried by the longitudinal growth of the intestine upward or downward." In Horgan's opinion, the accessory pancreas is formed as a result of the lateral buds of the pancreatic anlage attaching themselves to any organ with which they may be in contact and later being cut off from the main body of the pancreas by the growth and the change of relative position of the two organs.

Anatomically, the aberrant pancreatic nodules are firm yellowish-white irregular masses which vary in size from 2 or 3 mm. to as large as 4 or 5 cm. in diameter. They have been found all the way along the gastro-intestinal tract from the stomach to within a few centimeters of the cecum, as well as in the omentum, mesenteric fat, splenic capsule, gallbladder and umbilical fistula. In 62, or 33 per cent of the 186 reported cases, the nodules were found in the stomach; in 43, or 23 per cent, in the duodenum; in 40, or 21.5 per cent, in the jejunum, and in 30, or 16 per cent, in the ileum. In 178, or 95.7 per cent of the cases reported, the aberrant pancreas was found in the wall of the stomach or small intestine, usually in the muscularis but frequently in the submucous or subserous layer. In 33, or 17.7 per cent of the total series, the aberrant pancreas was in a diverticulum—in 3 cases this was found in the stomach, in 3 others in the duodenum, in 1 in the jejunum and in 26 in the ileum. In 13 cases of diverticulum of the ileum containing aberrant pancreas the diverticulum was reported as a true Meckel's diverticulum.

Histologically the general structure is such that the diagnosis is evident on microscopic examination. The pancreatic acini are usually normal in structure and arrangement and frequently contain granules of zymogen. Islands of Langerhans may or may not be present. In many reports there is no mention made of them; in others they are identified with difficulty, while in still others they are recorded as being

normal in size and number. The ducts, when mentioned, are described as being lined with the epithelium typical of pancreatic ducts and are scattered throughout the acini. They usually coalesce and open into the intestine, although some variations have been noted. According to Opie, they may open into the bile duct; according to Bean and Dreyer, they may occasionally open into the main pancreatic duct. Nicholson stated that they may be continuous with ducts lined by cells identical with those of Brunner's glands. The mucous membrane is usually typical of that portion of the intestine in which the gland is found, but in some cases it has been gastric or duodenal, whatever the location of the nodule. When the accessory pancreas was situated in the muscularis, its growth frequently thinned and separated the muscle fibers to such an extent as to produce a definite weakness in the intestinal wall.

Physiologically, the accessory nodules function like a normal pancreas, and many authors have described granules of zymogen in the acini and ducts filled with richly albuminous precipitate similar to that found in the ducts of a normal gland.

Clinically, it is interesting to note that although the majority of the known cases of accessory pancreas were found at autopsy and had apparently never produced clinical symptoms during life, the remainder had given rise to a large variety of surgical conditions, such as intussusception, in the cases of Brunner, Bize, Benjamin and Hulst; mechanical intestinal obstruction, in the case of Albrecht and Arzt, and in that of Clogg; umbilical fistula, in Wright's case; pyloric and duodenal ulceration, in the cases of Cohen and of Deaver and Reimann; pyloric obstruction, in the case of Hale and in those of Branham; carcinomatous changes, in the cases of Branham, in that of Bookman and in that of Semsroth; pancreatitis, in the case of Mayo Robson, and in those of Opie and Gibson; necrosis of fat, in one of Warthin's cases, and intestinal diverticulum, in the cases of Neumann, Nauwerck, Simon and others. In our case of Meckel's diverticulum containing aberrant pancreas and in that of Thomson the patient complained of symptoms simulating appendicitis. In neither case was the appendix sufficiently involved to account for the symptoms, and in each case the patient was completely relieved after removal of the diverticulum.

REPORT OF CASE

History.—H. J. M., aged 29, a geologist, was admitted to St. Vincent's Hospital on Jan. 31, 1932, complaining of pain in the lower right quadrant of the abdomen. Three days before admission he had suffered an attack of pain in the same region, severe enough to "double him up," which had lasted for two hours. There was nausea but no vomiting. The next morning there were tenderness and rigidity at the site of the pain. That evening he had a similar attack, not so severe as the first but of longer duration. He experienced no radiation of pain, and no urinary

symptoms or intestinal disturbances. Prior to the onset of this illness he had always been in excellent health.

Physical Examination.—The patient was a strong, healthy young man, weighing about 200 pounds (90.7 Kg.). Apparently he was not suffering severe pain. The systolic blood pressure was 112; the diastolic, 78; the temperature was 99.4 F. There were a slight rigidity and considerable tenderness on deep pressure over the lower right quadrant of the abdomen. The remainder of the examination gave negative results. The urine was reported normal except for a few pus cells. A roentgenogram of the kidneys, ureters and bladder showed no unusual condition. Hemoglobin was 70 per cent; leukocytes numbered 13,400, with 26 per cent lymphocytes and 74 per cent polymorphonuclears.

A diagnosis of subsiding subacute appendicitis was made, and appendectomy was advised. The patient was allowed to go home to complete some work, but he had another attack of pain the next day and returned to the hospital. A second physical examination gave the same results as the first, with the exception that the leukocytes had increased to 15,500 and there were 90 per cent polymorphonuclears.
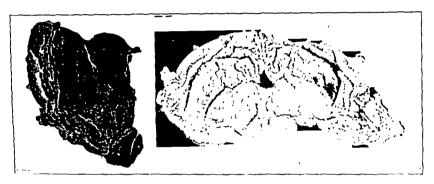
Fig. 1.—Gross appearance of the exterior and interior of a Meckel's diverticulum containing aberrant pancreas.

Operation.—The abdomen was explored on February 1, access being gained through a median right rectus incision. The appendix showed only a moderate amount of inflammatory reaction, which seemed insufficient to account for all the symptoms. Examination of the terminal part of the ileum revealed a Meckel's diverticulum 8 cm. in length, situated about 90 cm. from the ileocecal valve, with what appeared to be a subacute inflammatory process at its tip. The diverticulum and appendix were removed. The stomach, duodenum, gallbladder, right kidney and right ureter were normal. The pathologic examination was made by Dr. E. M. Hall of St. Vincent's Hospital.

Pathologic Examination.—The specimen examined consisted of a Meckel's diverticulum measuring 5 by 3 cm. (fig. 1). At the tip of the sac was a firm polyp-like growth of mucous membrane. The surface of the mucosa over this growth was coarsely granular. In the wall beneath the mucosa was a mass of opaque gray tissue of glandular appearance resembling pancreatic tissue, which measured 2 by 1.5 by 1 cm. In the wall of the diverticulum, forming the sides of the tube, all the layers of the normal bowel could be distinguished. The mucous membrane was rather thick. The muscularis measured about 1 mm. in thickness, and the circular and longitudinal layers could be identified with a hand lens.

Histologic Examination.—Sections of the nodule revealed glandular acini typical of those seen in the pancreas. The lobules were irregular in size and shape and appeared to be somewhat more cut up than in the normal gland. Separating many of the lobules were fasciculi of smooth muscle, indicating that the accessory glandular tissue was intramural. From two to five small islands of Langerhans could be seen in each low power field (fig. 2). These were composed
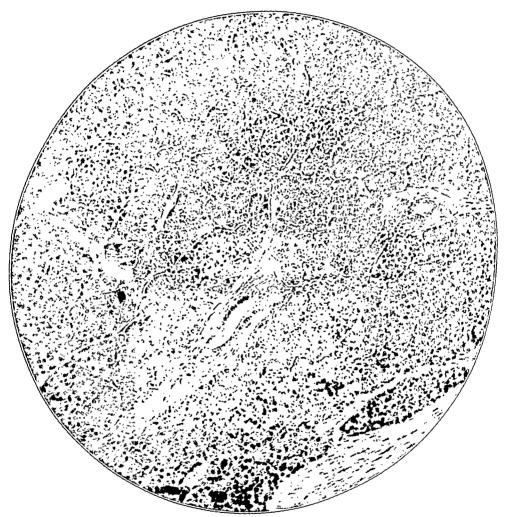
Fig. 2.—Low power magnification of a section of aberrant pancreas in Meckel's diverticulum, showing small islands of Langerhans.

of cells with extremely clear cytoplasm. Abundant ducts were found in the interlobular fibrous tissue. None of the ducts was dilated, so that it was evident that the secretion reached the lumen of the bowel.

The mucosa covering the accessory pancreas was distinctly hypertrophied. It was of considerable interest also because of its varied constituents. Along one edge of the section appeared fairly normal hypertrophic villi of the small intestine. These were very long and closely set and were covered with thick columnar epithelium having clear cytoplasm. There was a moderate number of rather inactive

goblet cells. The opposite side of the section showed a somewhat similar picture except that the villi were more or less edematous and contained numerous distended goblet cells. A considerable number of round cells and a few eosinophils were present in the supporting connective tissue of the villi (fig. 3).

The mucosa over the midportion of the growth showed the characteristics of gastric mucous membrane. The upper third was composed of short, broad villi
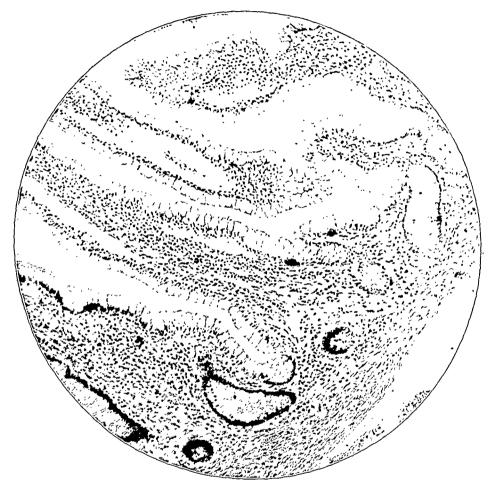
Fig. 3.—Section of mucosa covering an accessory pancreas, in which appear fairly normal hypertrophic villi of the small intestine.

covered with thick epithelium of much the same nature as that described in the preceding paragraph. The deeper two thirds was made up of irregular tubes lined with two kinds of cells: (a) a small cell with granular cytoplasm and (b) a much larger, plumper cell with bulging sides and clear vacuolated cytoplasm (fig. 4). These types of cells correspond closely with the chief and parietal cells of the gastric mucosa. Many round cells and eosinophils were present in the superficial portions.

Warthin, in 1904, Horgan, in 1921, and Simpson, in 1927, completely reviewed the literature and brought the list of the recorded cases of accessory pancreas up to date at the time of the writing of their respective papers. Table 2 shows the number of cases of accessory pancreas found by previous authors and by us and the locations. The
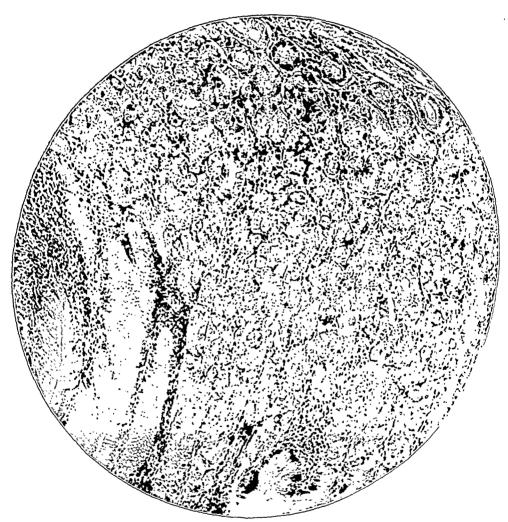
Fig. 4.—Section of mucosa covering an accessory pancreas, in which are shown chief and parietal cells of gastric mucosa.

discrepancy between the figures of our table and those of Simpson's may be explained by stating that in 6 cases the number of accessory pancreatic nodules was multiple—in 5 cases there were 2 accessory pancreatic nodules, and in 1 case there were 3 nodules. Simpson's table is based on the number of accessory pancreatic nodules, and ours, on the number of cases. The cases listed as occurring in Meckel's diverticula include all conditions claimed by the authors reporting them to be aber-

rant pancreas in a true Meckel's diverticulum, even though the reviewers did not list them as such.

Considerable controversy has arisen among many authors· as to whether the diverticula in which the pancreatic nodules were found were secondary diverticula, owing to the presence of the pancreatic nodules, or whether they were true Meckel's diverticula containing accessory pancreases. Opinion is about evenly divided. Kaufmann stated that a true Meckel's diverticulum is located opposite the mesenteric attachment about 1 meter above the ileocecal valve in adults (this may vary from 0.5 to 2 meters at the most) and about from 0.3 to 0.5 meter above the valve in the new-born. The size may vary, but is usually that of a finger. Sometimes the diverticulum has its own mesenteric attachment

TABLE 2.—*Instances of Accessory Pancreas Collected from the Literature*

Location	Warthin (1904)	Horgan (1921)	Simpson (1927)	Hunt and Bonesteel (1932)	Total	Per Cent
Wall of stomach	14	8	25	12	59	31.7
Wall of duodenum	10	4	14	12	40	21.5
Wall of jejunum	13	13	10	3	39	20.9
Wall of ileum	1	1	2	..	4	2.1
Wall of intestine (exact location not given)	1	1	1	..	3	1.6
Diverticulum of stomach	1	..	2	..	3	1.6
Diverticulum of duodenum	..	2	..	1	3	1.6
Diverticulum of jejunum	1	..	..	..	1	0.54
Diverticulum of ileum	2	3	4	4	13	7.0
..	3	1	6	3	13	7.0
..	1	..	..	..	1	0.54
..	1	..	..	..	1	0.54
Omentum	1	..	..	..	1	0.54
Splenic capsule	..	1	2	..	3	1.6
Gallbladder	..	..	1	1	2	1.1
Total number of cases	49	34	67	36	186	

with vessels from the omphalomesenteric vessels. According to Keen, Meckel's diverticulum occurs in about 2 per cent of all persons and may be located anywhere from 4 cm. to 4 meters from the ileocecal valve, but usually it is situated between 30 and 90 cm. from the valve. It is generally more than 2 cm. in length, and may have a direct connection with the umbilicus or may be united indirectly with vascular bands to the mesentery, intestines or umbilicus.

Zenker, in 1861, reported that he had found at autopsy in an adult a nodule of pancreas the size of a cherry pit in the fatty tissue around the apex of a true Meckel's diverticulum and communicating with the diverticulum only by means of a small duct. The diverticulum was 54 cm. from the ileocecal valve. He was of the opinion that under the circumstances it would have been impossible for the accessory pancreas to have been a causative factor in the production of the diverticulum. Albrecht and Arzt described a cordlike structure of connective tissue extending from the apex of a diverticulum and containing an accessory

pancreas, which they thought was a remnant of the omphalomesenteric duct and the presence of which they considered as definite proof that the diverticulum was a true Meckel's diverticulum. Koch and Suzuki examined 50 Meckel's diverticula at autopsy and found pancreatic tissue in 2 of them. Wright performed an operation on a child 12 years of age for a congenital umbilical fistula, which he found was due to an accessory pancreas draining through the umbilicus. This suggests that the accessory pancreatic nodules can become disseminated along the omphalomesenteric tract. Furthermore, among others, Schirmer, Eugen Albrecht, Merkel, Hedinger, Kaufmann, Nazari and Cogniauz described cases in which the pancreatic nodule was located in a diverticulum of the ileum, which they considered to be a true Meckel's diverticulum.

Neumann, Brunner, Bize, Simon, Robertson and Hulst reported cases of an accessory pancreas in a diverticulum of the ileum, which diverticulum they believed was the result of the presence of the accessory pancreas. In support of this view they urged that Meckel's diverticulum occurs in a definite location, and that in only a small percentage of the cases was the diverticulum found in such a location that it might be considered a true Meckel's diverticulum; also, that there have been cases in which the diverticulum containing pancreas has been found at any point along the gastro-intestinal tract from the stomach to within a few centimeters of the ileocecal valve. They explained the formation of the diverticulum by stating that a nodule of pancreas located in the musculature of the intestine could so spread and weaken the muscular coat during growth that the intra-intestinal pressure and the peristaltic traction on the nodule would produce a bulging or diverticulum at that particular point. In support of this argument Nauwerck's case was interesting in that two distinct diverticula were found, the proximal one at a distance of 230 cm. and the distal one at a distance of 80 cm. from the ileocecal valve. The proximal diverticulum contained pancreas; the distal one was a true Meckel's diverticulum and did not contain pancreas. The author pointed out the similarity of the two diverticula and stated that had he not found the second one he would have considered the diverticulum containing the pancreas a true Meckel's diverticulum. It is probably true that many of the diverticula containing an accessory pancreas are secondary to the presence of the accessory pancreas in the gastro-intestinal wall; however, as is fairly well proved by the cases reported by Wright, Albrecht and Arzt, Clogg, Koch and Suzuki and others, accessory pancreatic nodules may be disseminated along the omphalomesenteric duct and may be found in direct association with a true Meckel's diverticulum.

SUMMARY

The literature contains reports of 186 cases of accessory or aberrant pancreas; in 178 cases the aberrant pancreas was found in the stomach, duodenum, jejunum or ileum. For the most part the aberrant pancreas existed as a nodule in the normal gastro-intestinal wall. In 33 cases, however, it was found in a diverticulum of the stomach, duodenum, jejunum or ileum. In only 13 of these cases was the diverticulum classed as a true Meckel's diverticulum. The case herein reported is the fourteenth recorded case of a true Meckel's diverticulum containing pancreatic tissue.

RECORDED CASES OF DIVERTICULUM OF THE TERMINAL ILEUM CONTAINING ABERRANT PANCREAS

The situation of the diverticulum in the cases reported ranged from 10 cm. to 2.3 meters from the ileocecal valve. They may be cases of true Meckel's diverticulum but were not designated as such by the authors.

CASE 1.—Neumann, in 1870, found at autopsy in a boy, aged 10 months, a diverticulum 60 cm. above the ileocecal valve, to the apex of which an accessory pancreas the size of a pea was attached by a pedicle.

CASE 2.—Nauwerck, in 1892, found in a man, 43 years of age, a diverticulum 9 cm. long, located 2.3 meters above the ileocecal valve, in the apex of which there was an accessory pancreas. Another diverticulum which was found in the same patient, 80 cm. above the ileocecal valve, Nauwerck considered a true Meckel's diverticulum. The latter contained no pancreatic tissue.

CASE 3.—Brunner, in 1899, found at operation in a child, aged 4½, an intestinal obstruction resulting from the invagination of a diverticulum into the lumen of the ileum. The diverticulum was situated 37 cm. above the ileocecal valve and contained in its apex an accessory pancreas 22 mm. in diameter. Brunner was doubtful whether this was a true Meckel's diverticulum.

CASES 4 and 5.—Bize, in 1904, cited a case of Bize and Kirmisson, who had observed at autopsy following an operation for intussusception a diverticulum the size of the thumb, 25 cm. from the cecum, which contained a nodule of pancreas the size of a hazelnut.

Bize cited another case, of Bize and Grisel, in which was found at operation in a child, 6 years of age, a diverticulum 4.5 cm. long, situated 60 cm. from the ileocecal valve. The diverticulum was invaginated into the lumen of the ileum and contained in its apex an accessory pancreas the size of an almond.

CASE 6.—Simon, in 1905, found a diverticulum the size of a thumb 75 cm. above the ileocecal valve, in the apex of which there was an accessory pancreas.

CASE 7.—Thomson, in 1908, found at operation in a man, aged 33, a diverticulum 45 cm. above the ileocecal valve, which contained an accessory pancreas in its tip.

CASE 8.—Hulst, in 1909, found a polyp-like structure 2.5 cm. long, situated 10 cm. above the ileocecal valve, containing at its apex an aberrant pancreas 12 mm. in diameter. This structure represented an invagination of the intestinal wall. The author was doubtful as to whether or not it was a true Meckel's diverticulum.

RECORDED CASES OF TRUE MECKEL'S DIVERTICULUM CONTAINING ABERRANT PANCREAS

CASE 1.—Zenker, in 1861, found at autopsy in an adult a true Meckel's diverticulum. The diverticulum was shaped like a "finger of a glove." Embedded in the fatty tissue near its apex was an accessory pancreas.

CASE 2.—Schirmer, in 1893, found at autopsy in a boy, 3 years of age, a true Meckel's diverticulum shaped like a "finger of a glove." It was located 115 cm. from the ileocecal valve on the convex margin of the ileum and measured 8 cm. in length and 2.5 cm. in diameter; it had a small mesentery of its own. In the apex of the diverticulum was a small nodule of accessory pancreas the size of a bean.

CASE 3.—Albrecht, in 1901, found a true Meckel's diverticulum with a nodule of aberrant pancreas in its apex.

CASE 4.—Merkel, in 1905, found at autopsy a true Meckel's diverticulum 1.5 meters from the ileocecal valve, in the apex of which he found a "pancreatic embryo."

CASE 5.—Hedinger, in 1906, found at autopsy in a man, 36 years of age, who had died of heart trouble, a true Meckel's diverticulum 5 cm. long and located about 1 meter above the ileocecal valve on the convex surface of the intestine, in the apex of which he found a nodule of pancreas 2.5 by 0.5 cm. in diameter.

CASE 6.—Kaufmann, in 1907, reported a case in the Baseler Museum in which an accessory pancreas the size of a nut was found in the tip of a diverticulum located at the site corresponding to the location of a true Meckel's diverticulum.

CASE 7.—Clogg, in 1908, found at operation in a boy, 12 years of age, in whom symptoms of intestinal obstruction had developed immediately following a blow in the abdomen, a true Meckel's diverticulum ¾ in. (1.9 cm.) in length, in the end of which was a flat mass of pancreatic tissue ¾ in. in diameter.

CASE 8.—Nazari, in 1909, found at autopsy in a man, aged 35, who had died of hemorhage following perforation of a gastric ulcer, a true Meckel's diverticulum 5 cm. long and 1 cm. in width, located 1 meter above the ileocecal valve, in the apex of which there was a mass of pancreatic tissue 1 cm. in diameter.

CASE 9.—Albrecht and Arzt, in 1910, reported the case of a boy, 15 years of age, who had always had good health until three days before operation, when he was seized with pain resembling colic, which gradually increased, with the development of complete obstruction, fecal vomiting and visible peristalsis. At operation the intestine was found to be greatly distended and inflamed, and the abdomen contained turbid fluid. The obstruction was found to be due to a very tightly stretched cord of connective tissue, which was severed. One end of the cord was attached to the apex of a Meckel's diverticulum which contained an accessory pancreas. The attachment of the other end of the cord could not be found. Albrecht and Arzt believed this cord to be a remnant of the omphalomesenteric duct and were of the opinion that its presence was conclusive evidence that the diverticulum was a true Meckel's diverticulum.

CASES 10 and 11.—Koch and Suzuki, in 1912, examined 50 Meckel's diverticula at autopsy, in 2 of which they found accessory pancreatic tissue.

CASE 12.—Schaetz, in 1925, reported a case of Meckel's diverticulum containing pancreatic tissue in a girl, aged 27, who had died of pulmonary tuberculosis. Pancreatic tissue and the gastric type of mucous membrane were found in the diverticulum.

CASE 13.—Cogniauz, in 1928, found at operation for intussusception in a child, aged 4, an invaginated Meckel's diverticulum the apex of which contained an aberrant pancreas the size of a hazelnut.

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MECKEL'S DIVERTICULUM

REPORT OF A CASE OF HEMORRHAGE IN THE BOWEL ASSOCIATED WITH A MECKEL'S DIVERTICULUM THAT PRESENTED AN ADENOMA COMPOSED OF GASTRIC AND DUODENAL GLANDS

R. N. SCHULLINGER, M.D.

AND

A. P. STOUT, M.D.

NEW YORK

The case reported in this paper is of interest not only because it appears to be unique but also because it emphasizes two aspects of Meckel's diverticulum which have received some attention but are not yet sufficiently appreciated or emphasized. These considerations are, first, that Meckel's diverticulum rather frequently contains heterotopic alimentary tissue, and second, that the diverticulum may manifest itself clinically by bleeding, especially if it contains heterotopic gastric tissue, although this is not the only cause of bleeding. An analysis of the reported cases of bleeding Meckel's diverticulum with a discussion of the more probable causes of the hemorrhage will be given subsequently.

REPORT OF CASE [1]

History.—A boy, aged 16, American born, a high school student, had been in good health up to the onset of the illness to be described, with the exception of mild but persistent constipation associated with occasional vague, transitory pain in the upper part of the abdomen, during the past four years. While attending an exhibition on the afternoon of Nov. 30, 1929, he suddenly felt nauseated and went to a nearby drugstore, where he took some sodium bicarbonate, which he promptly vomited. At this time he felt a desire to defecate and had one small, but well formed, brown stool. On his way home he vomited four or five times and also experienced cramplike pain in the right side of his abdomen, which at first was constant, but later became intermittent, more severe, and finally paroxysmal. On his arrival at home he was taken with diarrhea. The first stools were watery, but these were soon followed by large bloody movements in which there was a small amount of mucus with bright red blood but not mixed with the blood. There was no history of a preceding dietary indiscretion. The family physician found the patient acutely ill and pale, with a pulse rate of 140 and a subnormal temperature. The extremities were cold, and the patient seemed to be in a state of shock. Hospitalization was advised, and he was immediately brought to the Presbyterian Hospital and admitted to the first surgical division.

Examination.—When first seen by one of us (R. N. S.), the patient was tall and rather thin for his age, and seemed acutely ill and in evident pain. His face was flushed. The pulse rate was 120; the blood pressure, 80 systolic and 60 diastolic, and the temperature, 103 F. by rectum; respirations were 28 per minute and entirely thoracic. The throat was slightly injected, and the heart, except for its rapid rate, was normal; the lungs were clear. The abdomen was scaphoid and symmetrical and presented no scars or rash. It did not move with respiration, and no peristaltic waves were noted. There was involuntary spasm over the whole right lower quadrant with associated tenderness. The point of maximum tenderness was slightly above and mesial to McBurney's point. Rebound tenderness was present over this same area, but no mass could be felt. Fluid wave, areas of shifting dulness and obliteration of liver dulness were absent. The rectal ampulla was empty, and no mass could be felt in the lumen above or impinging on the rectal wall. There was slight tenderness high up on the right side of the rectum. During the examination the patient had three very severe paroxysms of pain lasting about three minutes, then gradually subsiding. There was also one large bowel movement consisting of bright red blood *unmixed* with mucus. The red cell count was 4,700,000 and the white cell count 16,500 with 93 per cent polymorphonuclears. Urinalysis gave negative results.

The picture was unusual. There was nothing in the past history to suggest duodenal ulcer. The severe pain and prostration, with the signs pointing to the ileocecal region, suggested an intussusception, but in this condition bloody stools are supposed to occur only once or twice and in smaller amounts, while the blood is said to be *mixed* with the mucus. Volvulus was considered as another possibility, as well as a bleeding ulcerated intestinal polyp or perhaps an ulcer of the lower portion of the ileum or of the cecum. Acute colitis and the various dyscrasias of the blood were not seriously considered in view of the short history and the physical signs.

Because of the severity of the abdominal signs, together with profuse bleeding by rectum, fever and leukocytosis, operation was advised. This was also concurred with by Dr. William Barclay Parsons, Jr., who saw the patient in consultation with us. Meanwhile, general preoperative supportive measures were instituted. A preoperative diagnosis of ileocecal intussusception was made.

Operation.—Under nitrogen monoxide-oxygen anesthesia, the peritoneal cavity was entered through a middle right rectus incision. No free fluid or evidence of peritonitis was noted. The intestinal coils were not distended. The appendix was normal in position and appearance, and the ileocecal region revealed no evidence of a recent intussusception. The whole extent of the colon was carefully examined, and nothing abnormal could be seen or felt. The ileum was then followed from the cecum proximally, and about 3 feet from the ileocecal junction a segment of slightly distended intestine was encountered, through the walls of which could be detected reddish-brown material, presumably blood. About midway along this blood-containing segment of intestine a Meckel's diverticulum was found arising from the antimesenteric border, at right angles to the long axis of the intestine. It was about from 10 to 12 cm. in length, the circumference equaling that of the adjacent ileum. It coursed downward, forward and mesad, and the tip continued as a very thin, pale, delicate threadlike process which was attached to the anterior abdominal wall a little below the umbilicus. The diverticulum was not distended, nor did it appear to be acutely inflamed. Along the proximal half of its inferior surface there was noted the attachment of a mesenteriolum containing a single large blood vessel. The intestines were then carefully examined up to the duodeno-jejunal junction, and nothing abnormal could be detected. The mesentery of the

diverticulum was ligated and divided, after which the base of the diverticulum was clamped, cut and cauterized with invagination of the stump in purse string fashion. A few reenforcing seromuscular Lembert sutures were then placed around the site of inversion. The caliber of the adjacent intestine did not seem to be appreciably diminished. The appendix was also removed.

Postoperative Course.—The patient had a moderate reaction following the operation, the pulse remaining somewhat rapid for the following three days and the temperature gradually subsiding until it became normal on the third day. There was no nausea, vomiting or distention, and subsequent rectal treatments and bowel movements revealed no more evidence of blood. There was moderate pain from the wound, but nothing simulating the severe colicky pain felt previous to the operation. The wound remained clean and healed. The patient was out of bed on the thirteenth day and was allowed to go home on the twenty-first. Before his discharge from the hospital, an enema of barium sulphate was given and a series of roentgenograms of the gastro-intestinal tract were made. The former showed no delay in filling the colon and cecum, and the whole large bowel appeared to be normal. After evacuation there were no shadows suggesting diverticula. The series of roentgenograms revealed a normal, freely movable, nontender, medium-sized stomach. There was no delayed emptying time, and the outline of the stomach was regular. Under the fluoroscope, the duodenal bulb seemed irritable, but the films revealed no deformity or evidence of an organic lesion. At six hours there was a small collection of barium in the terminal ileum, but the roentgenologist was not certain whether this was at the site of the previously removed diverticulum or at the ileocecal junction. At twenty-four hours nothing abnormal was seen. Since the patient's discharge he has been seen from time to time, and at a visit made recently, twenty-seven months after operation, he looked well. His color was good, and he showed moderate development in stature. He complained, however, of constipation and cramplike pains on the left side of the abdomen, which he had had for the past three months. He had no symptoms referable to the scar, the umbilical region or the right lower quadrant. His appetite was good, there were no digestive disturbances, and at no time since the operation had he noticed bloody or tarry stools. Examination revealed that the patient was in good physical condition. He was obviously apprehensive and worried for fear that there might be some new serious malady lurking in his abdomen. Inspection of the abdomen showed nothing abnormal. The scar was well healed and firm. Palpation disclosed nothing unusual except tenderness in the left lower quadrant over the sigmoid, which could be felt. There were no other masses or tender areas. Rectal examination gave negative results. Analysis of the stool showed no evidence of blood, ova or parasites. An enema of barium sulphate revealed a normal colon except for rather marked spasm of the descending colon with slight diminution in the depth and number of haustrations when compared with the findings two years before. A series of roentgenograms of the gastro-intestinal tract and a study of the ileum were also made, and they failed to show any evidence of a gastric, duodenal, jejunal or ileal pathologic process. In view of these findings, it was thought that the patient's symptoms might be due to a spastic colon. He was therefore placed on a semibland diet and given moderate doses of sodium nitrite and tincture of belladonna. The response to this regimen was good, and two months later he was entirely symptom-free, whereupon the antispasmodic therapy was discontinued, and he indulged in a liberal, well balanced diet without ill effect. He was last seen Dec. 16, 1932, three years after his operation. He had been feeling extremely well, had gained considerable weight and was moderately active in athletics. His habits are excellent, and his bowels move regularly.

There are no abdominal pains, and he has no symptoms referable to his scar or former illness. Examination showed him to be in splendid condition. The abdomen was soft, and the scar was firm; no masses were felt, and there were no areas of tenderness. The follow-up result has, therefore, been most satisfactory.

Pathologic Examination.—The diverticulum, which had shrunken considerably after fixation in a diluted solution of formaldehyde, measured about 4 cm. in length. The peritoneal coat was smooth, but at one point showed some small nodular projections about 1 mm. in diameter. The remains of the threadlike adhesion could be seen at the tip (fig. 1, *B*). The diverticulum was bisected longitudinally, and the lumen seemed empty. The knife decapitated an isolated pedunculated tumor which sprang from one lateral surface of the mucous membrane in the distal portion over an area 4 mm. in diameter. It was rounded and slightly nodular, and measured 7 mm. in length, 5 mm. in width and 4 mm. in height. The mucous membrane of the diverticulum seemed to be pink and intact, and had many papillary elevations less than 1 mm. in diameter, which represented appar-
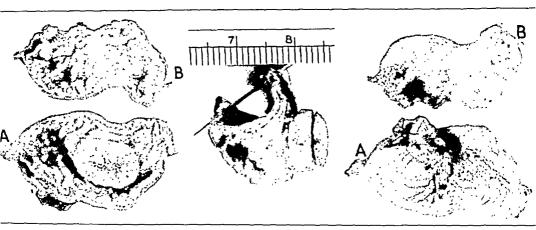
Fig. 1.—Photograph of a Meckel's diverticulum enlarged one and one-half times. At the right is shown the external surface with dilated subserosal vessels. *A* is the portion of the diverticulum which was attached to the ileum; *B*, the remnant of the adhesion at the tip. In the middle is shown the pedunculated adenomatous growth attached to the mucosal surface of the diverticulum. Its dome has been replaced after sectioning. Note the hyperplastic nodules of lymphoid tissue scattered over the mucosal surface of the diverticulum. At the left is shown a bird's eye view of the mucosal surface of the diverticulum after longitudinal section. The adenoma is shown in the lower half, bisected. The dark striations on the cut surface are engorged blood vessels.

ently hyperplastic lymphoid tissue. The tumor, on cross-section, appeared solid and pink and had numerous threadlike blood vessels radiating from the center toward the periphery. Sections taken through the wall of the diverticulum showed that it had the coats represented in the ileum, and that the glands were of the tubular mucous variety found there, shown in figures 2 and 5. The only changes from the normal that were recognized were the presence in the mucosa of an unusually large number of capillaries, somewhat dilated and congested. In the submucosa there were dilated, thin-walled veins and lymphatics. The former were widely distended with blood. Sections of the tumor showed that it was composed

of many tubular glands lined with cuboidal cells, among which could be recognized the chief and parietal cells which are typical of the glands of the stomach and a few characteristic Brunner's glands. The outer surface of the growth was covered with mucous glands. In the stalk or pedicle of the tumor there were dilated veins like those noted in the submucosa of the diverticulum. Further out in the tumor there were dilated capillaries filled with blood cells between almost every gland. A few red blood cells were found adherent to the surface of the growth. Figures 3 and 4 show the section under low and high power magnification, with Brunner's glands indicated at *A*. The growth, therefore, is a pedunculated adenoma composed of gastric and duodenal glands.

Fig. 2.—Low power photomicrograph of a longitudinal section through the wall of the diverticulum and the stalk of the adenoma. The stalk has a core of vascular submucosal fibrous tissue and is clothed as far as *A A'* with diverticulum mucosa. Beyond these points the adenoma proper begins.

A review of the literature has failed to reveal another example of gastric and duodenal gland adenoma of Meckel's diverticulum. In 1912, Lecène found an adenoma at the tip of a Meckel's diverticulum which lay in the submucosa and muscularis and was covered with intact mucosa, but this was composed of mucous glands resembling those of the intestine. Hertzler and Gibson found a small intramural mass at the apex of a Meckel's diverticulum composed of tubules resembling Brunner's glands. The superficial portion consisted of glandular tissue similar to pancreatic and intestinal glands. Bize also described a nodule

at the apex of a Meckel's diverticulum, situated in the submucosa and muscularis. It presented a picture of pancreatic glands, but certain portions of the nodule were the seat of glandular new growth arising from the ducts and having the characteristics of adenoma. "One may see the large ducts lined with cylindrical epithelium branching into a variable number of secondary ducts which are very short and terminate in the large cul-de-sacs of adenomatous tissue." He did not state whether the adenomatous portions of the tumor resembled gastric or
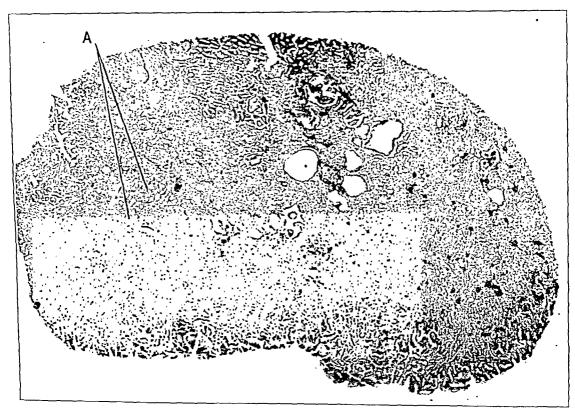
Fig. 3.—Low power photomicrograph of a cross-section through the adenoma taken at right angles to the axis of the pedicle. The entire periphery of the section is covered with a layer of mucous glands. Mucous glands also appear at intervals through the central portion, forming dilated cystic cavities lined with columnar goblet cells. The many tiny round acini forming the bulk of the central part of the section are simple gastric glands. At *A* are shown groups of Brunner's glands.

intestinal glands. Other neoplasms which have been reported include polyps, lipomas, myomas, angiomas, myxomas, sarcomas, carcinomas and carcinoids, but none of these has had gastric or duodenal elements in them. There is no occasion for surprise that an adenoma of the
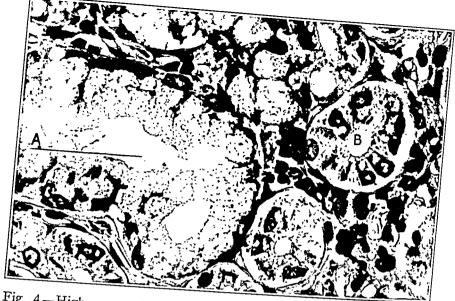
Fig. 4.—High power photomicrograph of the adenoma showing at *A* one of Brunner's glands and at *B* a simple gastric gland. The acinus is lined with chief cells and at the left is a parietal cell with larger granules in the cytoplasm.
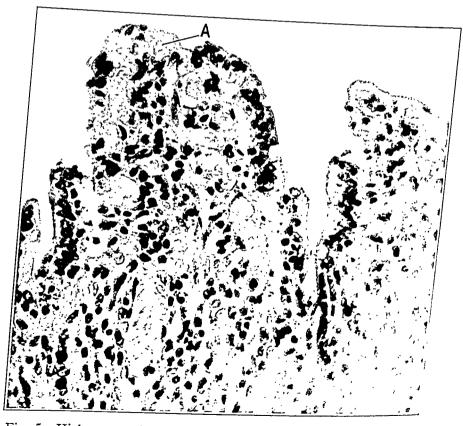
Fig. 5.—High power photomicrograph showing a fold of the mucosa of the diverticulum containing an unusually large number of capillaries. In some places, as at *A*, these are separated from the lumen only by the thinnest of membranes.

gastric type should be found in this situation, because heterotopic gastric and pancreatic tissue has frequently been noted in the diverticulum, and adenomatous growths composed of these tissues have been found in other parts of the alimentary tract. In connection with external fistulas of the umbilicus, adenomas have been described which usually are covered with mucosa of the intestinal type but sometimes are covered, in whole or in part, with gastric mucosa, and even may have gastric gland adenomas within their central portion. It is our belief (and the belief of others) that Meckel's diverticulum and these umbilical fistulas and polyps are persisting remnants of the vitelline (omphalo-mesenteric) duct. We have wondered why these structures have sometimes contained apparently heterotopic tissue, and in searching for an adequate hypothesis we have been compelled to review the whole question of alimentary heterotopia. We propose to discuss this question in a subsequent paper.

CLINICAL FEATURES

Bleeding from Peptic Ulcer of Meckel's Diverticulum.—The outstanding clinical feature of the present case, namely bleeding, merits some discussion, because bleeding from a Meckel's diverticulum is usually associated with an ulcer of that embryonic remnant. This has been emphasized by numerous observers, and more recently the recorded cases have been reviewed and summarized by Aschner and Karelitz, Lindau and Wulff and Greenwald and Steiner, the last named investigators, however, having included other lesions of Meckel's diverticulum as well. By combining the tabulations of these three groups of observers with subsequent case reports, we have been able to list sixty-eight cases.[2] They have been placed in two main groups, namely, the group

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2. We do not think that cases 8, 19, 32 and 37 in Lindau and Wulff's list should be accepted. Cases 8 and 37 are self-explanatory on consulting their table. Case 19 (Taylor) was not found after careful study of his paper. Case 32 was not accepted because the pathologic process was found in a large congenital diverticulum, whereas Meckel's diverticulum, which was also present, revealed no pathologic process. We were unable to obtain the references for cases 20 and 21, but we accepted these. Zimmermann's case is doubtful, because in his description an acute inflammatory process of the whole diverticulum is indicated, and it is possible that the ulcer might have resulted from this rather than from the more chronic localized lesion with which we are wont to associate peptic ulcer. For the same reason Hudson and Koplik's three cases are probably doubtful, and they state this in their paper. Winkelbauer's seventh case is also questionable as the bleeding may have occurred from the intussusception. Hess and Rosenblum's case is the same as case 2 of Abt and Strauss. Recently Borrmann reported a case of a large Meckel's diverticulum, 66 cm. long, in a boy of 14 who died of intestinal hemorrhage. At autopsy, an ulcer was found in the intestine close to, but not at the opening of, the diverticulum. We therefore did not include this case.

TABLE 1.—*Peptic Ulcer of Meckel's Diverticulum, Mucosa Investigated*

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Denecke........	1902	7	M	Absent	Perforation at base of diverticulum; no gastric mucosa found	Died (operation, autopsy)
Hilgenreiner...	1903	18	M	Present	Ulcer near tip of diverticulum at margin of intestinal mucosa; gastric mucosa present ?	Recovery
Deetz..........	1907	9	M	Absent	Perforated ulcer at base; gastric mucosa and pancreatic tissue	Recovery
Hübschmann..	1913	4½	M	Present	Perforated ulcer at base at margin of gastric mucosa	Died (operation, autopsy)
Gramen........	1915	10	M	Not stated	Perforated ulcer at base at margin of gastric mucosa	Recovery
Callender......	1915	19 mo.	Not stated	Present	Ulcer at border of diverticulum and ileum; eroded vessel at margin; gastric mucosa	Died (autopsy, no operation)
Meulengracht..	1918	12	M	Present	Penetrating ulcer near tip in intestinal mucosa; gastric mucosa close by inside pocket	Died (autopsy, no operation)
Müller..........	1919	11	M	Present	Perforated ulcer at midportion in intestinal mucosa; gastric mucosa also present	Recovery
Mégevaud and Dunant	1922	28	M	Present	Ulcer at base at border of gastric mucosa; eroded artery	Recovery
Brasser........	1924	15	M	Present	Perforated marginal ulcer; gastric mucosa	Died (operation, autopsy)
Humbert.......	1924	11 mo.	M	Present	Perforated ulcer near apex, adjacent to gastric mucosa	Died (operation, autopsy)
Guibal.........	1924	14	M	Present	Penetrating ulcer near base adjacent to gastric mucosa; three eroded arteries	Recovery
Pascale........	1925	41	F	Present	Perforating ulcer in midportion; gastric mucosa present	Recovery
Ulrich..........	1925	8 mo.	M	Present	Perforated ulcer in intestinal mucosa; gastric mucosa present	Died (operation, autopsy)
Abt and Strauss Case 1	1926	20 mo.	F	Present	Ulcer near apex; gastric mucosa at apex	Recovery
Etchegorry....	1926	16	M	Present	Perforated ulcer between gastric and normal mucosa	Recovery
Kleinschmidt... Case 1	1927	15	M	Present	Perforated ulcer near base; gastric mucosa	Recovery
Jackson, A. S..	1927	14	M	Present	Ulcer at border of gastric mucosa; correct preoperative diagnosis	Recovery
McCalla........	1927	4	M	Present	Perforated ulcer at base; gastric mucosa	Died (autopsy, no operation)
Büchner........	1927	24	M	Not stated	Ulcer at base between gastric and intestinal mucosa	Died
Gramen........	1927	11	F	Not stated	Peptic ulcer; gastric mucosa ?	Recovery
Gramen........	1927	21	M	Not stated	Peptic ulcer; gastric mucosa ?	Recovery
Meiss..........	1928	2	M	Present	Ulcer near tip at border of gastric mucosa	Recovery
Hartglass......	1928	4	F	Absent	Perforated ulcer at base at margin of gastric mucosa	Recovery
Peterman and Seeger	1928	6	M	Present	Penetrating ulcer at base; gastric mucosa; correct preoperative diagnosis	Recovery

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Franke.........	1929	Not stated		Not stated	Ulcer in intestinal mucosa; gastric mucosa at tip	Died
Winkelbauer... Case 6	1929	2	M	Present	Ulcer at base in normal mucosa; gastric mucosa close by	Recovery
Treplin.........	1929	Not stated		Not stated	Ulcer in normal mucosa; gastric mucosa	Recovery
Winkelbauer... Case 7	1929	19 mo.	M	Present	Ulcer with eroded vessel; no heterotopia; invagination of diverticulum with intussusception as well	Recovery
Aschner and Karelitz Case 1	1930	15 mo.	F	Present	Penetrating ulcer at base at margin of gastric mucosa	Recovery
Aschner and Karelitz Case 2	1930	26 mo.	M	Present	Ulcer at base adjacent to gastric mucosa	Recovery
von Haberer... Case 1	1930	13	M	Present	Ulcer near tip adjacent to gastric mucosa	Recovery
von Haberer... Case 2	1930	21	M	Present	Ulcer at base adjacent to gastric mucosa	Recovery
Schmidt.........	1930	18	M	Not stated	Two ulcers at border of gastric mucosa; one had perforated	Recovery
Fevré, Patel and Lepart Case 1	1930	7	M	Absent	Perforated ulcer at base at border of duodenal mucosa which lined the diverticulum	Recovery
Fevré, Patel and Lepart Case 2	1930	5 mo.	M	Present	Perforated ulcer at base at border of gastric mucosa	Recovery
Green......... Case 4	1930	6½ mo.	M	Present	Large diverticulum 40½ inches long with dilated bulbous end, separated from rest of diverticulum by a constriction; perforated ulcer in tip; 3 ulcers found 12 inches from distal extremity; tip lined with pyloric mucosa; gastric mucosa also found at site of other ulcers; elsewhere diverticulum lined with intestinal mucosa	Died (operation, no autopsy)
Büchner.........	1931	8	F	Not stated	Ulcer at border of gastric mucosa	Recovery
Lindau and Wulff Case 1	1931	15	M	Absent	Perforated ulcer near tip in normal mucosa; polyp contained gastric mucosa	Died (operation, autopsy)
Greenwald and Steiner Case 1	1931	15 wk.	M	Present	Perforated ulcer at base; gastric mucosa; correct preoperative diagnosis	Died (operation, no autopsy)
Greenwald and Steiner Case 2	1931	10	M	Absent	Perforated ulcer at base; gastric mucosa	Recovery
Cobb...........	1931	18	M	Present	Perforation near base at border of gastric mucosa	Recovery
Debré, Bopp and Semelaigne	1931	17 mo.	M	Present	Ulcer at base which had perforated into transverse colon; inflammatory reaction immediately around it, but no general peritonitis; diverticulum lined with gastric mucosa	Died (operation, no autopsy)
de Vernejolel...	1932	5	M	Present	Perforation at base with surrounding zone of induration; ulcer at border between gastric and intestinal mucosa	Recovery
Hudson and Koplik Case 13	1932	6	M	Present	Perforation of diverticulum, with peritonitis; ulcer at junction of gastric and intestinal mucosa	Died (operation, no autopsy)

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Hudson and Koplik Case 25	1932	5	F	Present	Perforation at base, with peritonitis; ulcer in intestinal mucosa at junction with gastric mucosa; resection of diverticulum	Recovery
Hudson and Koplik Case 31	1932	5	M	Present	Sigmoid distended with blood; ulcer found on microscopic examination; gastric and intestinal mucosa	Recovery
Mason and Graham	1932	9 mo.	M	Present	Excision of diverticulum; most of it lined with gastric mucosa; pancreatic tissue at tip; ulcer at border between gastric and intestinal mucosa, but involving the gastric mucosa	Recovery
McKeen	1932	53	M	Present	Ulcer near tip which had perforated and was adherent to ascending colon and surrounded with adhesions; diverticulum lined with intestinal mucosa	Recovery
Schaaf	1932	7	M	Present	Bloody peritoneal exudate; intramesenteric diverticulum 60 cm. long running parallel to ileum; perforation of diverticulum about midway close to mesenteric attachment of ileum; gastric mucosa lined distal two thirds of diverticulum; ulcer in gastric mucosa at site of perforation; correct preoperative diagnosis	Recovery
Vaughan and Singer	1932	7	M	Absent	Perforated ulcer near tip between gastric and intestinal mucosa, located in intestinal side	Recovery
Roudil and Marty	1932	7	F	Absent	Perforated ulcer at tip; necrosis of mucosa at distal end; author states necrotic mucosa impresses him as gastric	Died (operation, no autopsy)

Total = 52 cases

in which the mucosa was examined microscopically (table 1) and the group in which microscopic examination of the mucosa was lacking (table 2). There was no designation of sex in four cases; only ten of the patients were females, and the rest, fifty-four, or 85 per cent, were males. The average age of sixty-six patients (ages not stated for two) was 10.4 years; forty-two were 10 years or under (63 per cent) and fourteen were between 11 and 20 years of age (21 per cent), so that a total of fifty-six, or 84.5 per cent, of the patients were in the first two decades of life. The oldest patient was 53. Twenty-one died, making a mortality of 30 per cent. In thirty-five the ulcer had perforated, resulting in diffuse or spreading peritonitis, so that it is not surprising to learn that fifteen of these patients died. In other words, of twenty-one patients in the group with ulcer who died, fifteen died as a result of perforation of the ulcer. Bleeding was present in fifty-one, or 75 per cent, of those with ulcer (absent in seven and not mentioned for ten). In all but seven of the cases listed in table

1, gastric mucosa was microscopically identified. One of the seven excepted diverticula contained duodenal mucosa (Fevre, Patel and Lepart's first case); three others revealed normal intestinal mucosa (Winkelbauer, case 7, McKeen, and Denecke), and in three the character of the mucosa was doubtful (Gramen, two cases; Roudil and Marty, one case). A correct preoperative diagnosis of ulcer of Meckel's diverticulum was made in only six instances, namely, in A. S. Jackson's case, by the family physician, Dr. Ketterer (who also attended R. H. Jackson's patient of several years previously); in the case of Peterman and Seeger; in case 2 of Shanon; in the case of Schwarz and Daly; in case 1 of Greenwald and Steiner, and in the case of Schaaf. Aschner and Karelitz's first case, Coleman's third case and Brennecke's fifth case were all diagnosed as "Meckel's diverticulum," while Wolfson and Clurman correctly diagnosed a case of acute Meckel's diverticulitis. Lately Hudson and Koplik made a correct preoperative diagnosis twice (cases 29 and 32), and Faust did likewise in his second case. The fact that almost four times as many cases of ulcer of Meckel's diverticulum have been reported in the six years following Stulz and Worringer's collection of fourteen cases in 1926 makes it evident that this condition is being more widely appreciated and physicians will therefore be better able to recognize it preoperatively in subsequent cases.

The ulcer usually resembles in structure the peptic ulcer of the stomach or of the duodenum. It is often situated at the border between the two types of mucosa and consequently near the base of the diverticulum. In a certain number of these marginal or border ulcers the lesion will be found in the end-zone of the normal mucosa, but the edge of the ulcer will extend to the line of division between the normal and the heterotopic mucosa. Sometimes the ulcer is found completely in the intestinal mucosa of the diverticulum, a short distance from the heterotopic area. In still other instances the ulcer is located entirely within the aberrant tissue, and therefore this type of ulcer may be found at or near the tip of the diverticulum.

The bleeding in this group, when it occurs, appears usually as blood *unmixed* with mucus in the stools. This, together with the absence of a palpable mass, is considered a rather important differential point in distinguishing this condition from intussusception. In addition, the bloody stools are apt to be more frequent and greater in amount, whereas in intussusception one may obtain a history of only two or three small movements disclosing blood *mixed* with mucus or just some blood-stained mucus on the examining glove. Some of the patients in this group gave an account of repeated hemorrhages, preceded sometimes by slight constipation and associated with vague generalized

abdominal or periumbilical pains. Such episodes might occur over a relatively long or short period of time with intervals of months or years between them. The signs may therefore vary considerably, but the histories in many of the cases indicated that the patients were moderately, if not acutely, ill, that they were sometimes strikingly anemic, and that when the hemorrhage was profuse or if perforation of the ulcer had taken place, they exhibited a certain degree of shock.

Table 2.—*Peptic Ulcer of Meckel's Diverticulum, Mucosa not Investigated*

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Brentano	1904	21	M	Not stated	Perforated ulcer	Recovery
Läwen	1909	23	M	Not stated	Perforated ulcer near base; eroded artery	Recovery
Griffith	1914	19 mo.	M	Present	Perforated ulcer at tip; peridiverticular abscess	Died (autopsy, no operation)
Jackson, R. H.	1924	10	M	Present	Ulcer at base; eroded artery	Recovery
Schreuder	1925	8	M	Present	Pancreatic tissue at tip; ulcer at base; eroded artery; patient also had a duodenal ulcer	Recovery
Stulz and Woringer Case 1	1926	4	M	Present	Perforated ulcer at base	Died (operation, no autopsy)
Stulz and Woringer Case 2	1926	11 mo.	M	Present	Perforated ulcer at base, with abscess at site of perforation	Died (autopsy, no operation)
Abt and Strauss Case 2	1926	11 mo.	M	Present	Ulcers at tip	Recovery
Moore Case 2	1926	9 mo.	M	Present	Ulcer at base	Recovery
Moll	1926	5 mo.	Not stated	Present	Two ulcers at base of large diverticulum, 33½ inches long	Died (operation, autopsy)
Fuss	1927	37	F	Present	Bleeding ulcer near fundus, extending to muscular coat	Recovery
Kleinschmidt Case 2	1927	45	M	Present	Perforated ulcer	Recovery
Shanon Case 2	1928	18 mo.	F	Present	Perforating ulcer with attachment to bladder; correct preoperative diagnosis	Recovery
Smith and Hill	1929	14 mo.	M	Present	Perforated ulcer at tip	Recovery
Schwarz and Daly	1929	8	M	Present	Ulcer with large eroded artery at base; correct preoperative diagnosis	Recovery
Walters and Wilkins	1932	20	M	Present	Perforated ulcer near base	Died (operation, autopsy)

Total = 16 cases

In those cases in which signs of an acute abdominal lesion are lacking, the situation is often misleading, and Gray made the pertinent observation that acute lesions of Meckel's diverticulum may transform a picture of relatively good condition and well-being into one of sudden acute illness with signs of peritonitis and even shock. At operation, one may find perforation of the ulcer or evidence of severe hemorrhage into the adjacent intestinal coils. In a recent article, Vaughan and Singer also stated that the onset of symptoms may be gradual or

sudden. They emphasized the fact that sudden severe pain in the lower part of the abdomen, especially in children, associated with rigidity, leukocytosis and signs of beginning collapse or shock should lead one to suspect a perforated Meckel's diverticulum. They pointed out that in acute appendicitis, as a rule, the signs of acute diffuse peritonitis from perforation are apt to develop only after several hours, perhaps a day, following the initial symptoms. The tendency to spontaneous sealing of the perforation of a Meckel's diverticulum is also mentioned by them.

In the discussion of ulcer of Meckel's diverticulum, Fevré, Patel and Lepart emphasized the following points: 1. A young man with a history of recent hemorrhages by rectum followed by a picture of acute peritonitis (at which time the surgeon is usually called) must always make one suspicious of a perforated ulcer of Meckel's diverticulum. 2. With a history of bleeding of unknown origin, one must never close an abdomen without searching for Meckel's diverticulum. 3. If one operates for intestinal hemorrhage and Meckel's diverticulum is found, it should be removed regardless of its outwardly harmless and grossly normal appearance (this was certainly true in our case). 4. In any case of gastro-intestinal bleeding in infants or boys, when the cause is not determined, celiotomy should be performed before the signs of acute disaster develop. 5. It is important to search for a Meckel's diverticulum as the possible cause of peritonitis of undetermined origin. 6. Finally, it is important to seek a Meckel's diverticulum when the operative findings are not in accord with the preoperative diagnosis.

Mondor even goes so far as to state that in a proved case of acute appendicitis, if there has been a previous history of intestinal bleeding of undetermined source, one should examine the ileum for a Meckel's diverticulum, and if it is found, the diverticulum as well as the appendix should be removed. We are not in agreement with this statement because of the danger of spreading an otherwise localized peritonitis.

Bleeding from Causes Other Than Ulcer or Invagination of Meckel's Diverticulum.—We have found a number of instances in the literature (table 3) in which bleeding from a Meckel's diverticulum developed in connection with lesions not associated with ulcer or invagination, and yet it frequently appeared as the presenting symptom. This is certainly true of the case we report in this paper. There was no ulcer in the diverticulum, and the lining mucosa seemed to be intact. Even the surface of the adenoma revealed no break in continuity. The cases of Webster, Mayo and Johnson, Abt and Strauss (case 3) and Brennecke (case 5) presumably showed no interruption of the normal lining mucosa. Of still greater interest to us are those diverticula listed in table 3 which revealed heterotopic tissue without macroscopic interruption of the mucosal continuity, in spite of the clinical occurrence

Author	Year	Age, Years	Sex	Comments	Result
Webster..............	1902	42	F	Bloody stool once; diverticulum in left inguinal hernia	Recovery
Brennecke.............. Case 5	1913	25	M	Recurrent bleeding by rectum; diverticulum filled with blood; mucosa thick, pale, redundant, firm; no ulcer noted; no acute inflammation; no microscopic report; preoperative diagnosis of "Meckel's diverticulum"	Recovery
Stern.............. Case 16	1917	3	M	Repeated bloody stools; perforation of diverticulum with ulcerative phlegmonous process of the whole diverticular wall; diffuse peritonitis	Died
Mayo and Johnson....	1926	15	M	Repeated bleeding by rectum; ileum thickened above and below diverticulum, which was swollen and edematous	Recovery
Stone, J. B.	1926	14 mo.	Not stated	Bleeding; pancreatic tissue in wall of diverticulum; mucosa that of ileum	Died
Abt and Strauss....... Case 3	1926	11 mo.	M	Repeated hemorrhage by rectum; large diverticulum, 18 inches long, in mesentery of intestine; no heterotopia or ulcer found	Recovery
Rowan................. Case 2	1926	Not stated	M	Attacks of bleeding by rectum; at second operation diverticulum was found with perforation and a papilloma; cause of perforation not stated	Recovery
Tisdall.................	1928	11 mo.	M	Marked anemia; bloody stools; died of bronchopneumonia; large diverticulum in mesentery; gastric mucosa found but no ulcer	Died
Hürtling................	1928	64	F	Bleeding by rectum; myoma of diverticulum found	Recovery
Harrington............	1929	67	M	Mass of intestinal coils matted down between bladder and rectum; in midst of these coils inflamed diverticulum was found with perforations into several loops of intestine, bladder and rectosigmoid	Recovery
Faust and Walters....	1931	62	M	Recurrent bleeding by rectum; fibrosarcoma at tip of diverticulum measuring 9 by 7 by 5 cm. and adherent to dome of bladder	Recovery
Hudson and Koplik.... Case 2	1932	1½	M	Bleeding diverticulum with hemorrhage into lumen of adjacent intestine; no pathologic report	Recovery
Hudson and Koplik.... Case 15	1932	2 mo.	M	Blood on rectal examination; obstruction from fibrous cord running from tip of diverticulum to mesentery of ileum; release of obstruction; resection of diverticulum	Recovery
Hudson and Koplik.... Case 16	1932	10	F	Bloody diarrhea; blood in intestine and diverticulum; latter showed gastric mucosa, which appeared intact; capillary extravasation in mucosa; no ulcer	Recovery
Hudson and Koplik.... Case 17	1932	6	M	Bloody "tissue" in stools; obstruction from diverticulum adherent to mesentery overlying and constricting ileum; resection	Recovery
Hudson and Koplik.... Case 18	1932	13 mo.	F	Profuse hemorrhage by rectum; diverticulum found; not resected	Recovery (improved)
Hudson and Koplik.... Case 20	1932	1¼	F	Profuse hemorrhage by rectum; gastric and intestinal mucosa in diverticulum; resection; no mention of ulcer; considerable recent hemorrhage in all layers	Recovery
Hudson and Koplik.... Case 29	1932	9½	F	Old and fresh blood in stools; tip of diverticulum adherent to mesentery; ileum matted together about diverticulum by adhesions; gastric mucosa; resection; no ulcer; enterostomy; correct preoperative diagnosis	Recovery

TABLE 3.—*Meckel's Diverticulum with Bleeding from Causes Other Than Peptic Ulcer or Invagination—Continued*

Author	Year	Age, Years	Sex	Comments	Result
Hudson and Koplik.... Case 32	1932	5½	F	Bleeding by rectum; acutely inflamed diverticulum; gastric mucosa; no ulceration; correct preoperative diagnosis	Recovery
Faust.................. Case 1	1932	67	M	Previous attack of pain in lower part of abdomen associated with diarrhea and several passages of dark blood; distended diverticulum with narrow neck; perforation into bladder and sigmoid wall; abscess walled off by surrounding loops of ileum	Recovery
Faust.................. Case 2	1932	61	M	Several episodes of profuse hemorrhage by rectum; then signs of ileus; diverticulum composed of inflammatory mass obstructing one of ileal loops; many adhesions from adjacent coils; correct preoperative diagnosis	Recovery
Stout and Schullinger	1933	16	M	Profuse hemorrhage; adenoma of diverticulum composed of gastric and duodenal glands; no ulcer found; mucosa intact	Recovery

of bleeding, because they seem to lend support to our observations as to the source of the bleeding in our own case (J. B. Stone, Tisdall, Hudson and Koplik, cases 16, 20, 29 and 32). The case reports of Härting, J. B. Stone, and Faust and Walters indicate that certain tumors may be the source of bleeding from Meckel's diverticulum.[3] In the remaining cases listed in table 3 there was also exhibited bleeding from pathologic conditions of the diverticulum other than ulcer or invagination. Here again, in this group, the associated symptoms fail to disclose any similarity with the exception, perhaps, of abdominal pain. It appears, then, from the study of table 3, that bleeding can and does take place in processes other than ulcer or invagination of this embryonic remnant, and that it can occur apparently even in the presence of grossly intact normal and heterotopic mucosa. This has recently been emphasized by Hudson and Koplik.

Bleeding from Invagination With or Without an Associated Intussusception.—A few cases (table 4) have been chosen simply to illustrate that bleeding may also take place in connection with invagination of the diverticulum into the intestine with or without an associated intestinal intussusception. When bleeding results from invagination of the diverticulum alone, without any intussusception of the intestine proper, the bleeding may be attributed to the diverticulum, especially to the mucosa at the base of the diverticulum.

3. We did not include in table 3 Michaels' recently reported case of tuberculous ulcer of Meckel's diverticulum, because the bleeding may have originated from the tuberculous process involving the ileocecal region and the hepatic flexure.

We hesitate, therefore, to consider the group of cases of ulcer (tables 1 and 2) as a distinct clinical entity because our own patient, displaying most of the signs of bleeding ulcer of Meckel's diverticulum, failed to disclose any ulcer; the lesion was an adenoma instead. That there have been other instances in which the conditions simulated ulcer with bleeding is clearly shown in tables 3 and 4. We believe, then, that whereas ulcer is probably the commonest cause of bleeding from Meckel's diverticulum, there are other pathologic processes of that embryonic remnant which may produce a similar picture.

Other Clinical Symptoms and Signs in Connection with Lesions of Meckel's Diverticulum.—In addition to the occurrence of bleeding, a history of a slowly healing umbilicus or a persistent sinus at the umbilical region for a varying time after birth may also have some significance. Varying periods of constipation associated with vague, indefinite general abdominal or periumbilical pains are described in some of these cases. It has also been pointed out that persons with Meckel's diverticulum are apt to disclose other anomalies, such as harelip, cleft palate, dextrocardia, patent interventricular septum, meningocele, exstrophy of the bladder and incompletely rotated cecum. Christie found at autopsy congenital anomalies in one third of his sixty-three cases of Meckel's diverticulum. Symptoms may develop in the first months of postnatal life, more often in childhood, and even in the later periods of life, but in the great majority of cases symptoms are produced in the first two decades.

General Aspects of Meckel's Diverticulum.—The diverticulum may remain latent and symptomless throughout life. It has been found at from 2 to 3 per cent of all autopsies, and is about four times as common in males as in females, although ratios have been given as low as 2:1 and as high as 6:1. Of the sixty-eight diverticula showing peptic ulcers, all but nine certain and four questionable ones were found in males.

It is rare to find two or more cases of Meckel's diverticulum in the same family. It has been stated that in the group with ulcer, at least, the pain is not so sudden or so severe as in acute appendicitis, nor is the vomiting so constant or so persistent. Gray pointed out that acute Meckel's diverticulitis often starts during a period of body activity and exertion, while acute appendicitis frequently begins at night with the body at rest. Its position among the coils of the intestines probably renders it more dangerous than acute appendicitis, in which the process ordinarily seems to become localized more readily. The white blood cell count is often elevated, with a rise in the number of polymorphonuclear cells. The abdomen may be soft, but it is usually splinted in the umbilical and ileocecal regions. One may sometimes appreciate a palpable mass, but

not usually, unless there is an associated intussusception or an inflammatory mass with abscess formation. In determining the presence of a mass or a collection of exudate the rectal examination may furnish some information. Finally, one should note any abnormality of the umbilical cicatrix and the presence of meteorism around the region of the umbilicus, as well as any evidence of the anomalies previously mentioned.

With the passage of time, clinicians, especially pediatricians and surgeons, will become more impressed with the fact that a Meckel's diverticulum may be a cause of obscure abdominal symptoms, particularly in connection with bleeding, and even of acute abdominal conditions of undetermined origin, and therefore its existence will be discovered in the course of exploratory celiotomies more frequently. An illustration of this point is brought out by Baker, who, in 1930, found four cases of Meckel's diverticulum in the course of 150 laparotomies performed in a period of three months. Contrast this with McGlannan's observation, in 1922, that Meckel's diverticulum had been noted only three times in about 1,400 abdominal operations.

The general pathology of Meckel's diverticulum and its embryology have been thoroughly set forth by such authors as Fitz, Halstead, Eisendrath, Gray, Cheyne, Keith, Hilgenreiner, Cullen, Tillman, Waegeler, and Kelly and Hurden, and the reader who may be interested in these phases of the subject will find appropriate bibliographies at the close of the present paper.

In general, operative intervention is usually indicated because of the frequent existence of an acute abdominal condition. When the patient is very sick, it is better to temporize an hour or two in an effort to institute certain preoperative supportive measures. The operative procedure naturally depends on the lesion that is found. It would seem to be wiser to remove the diverticulum, provided one is not pressed for time and provided that its removal will not produce too much damage to the surrounding viscera and possibly favor a spread of infection if this is present. The mortality in the patients with acute inflammatory lesions was 40 per cent. In the patients in whom intussusception was caused by the diverticulum, the mortality was 60 per cent according to Gray and 68 per cent according to Halstead. In infants under 1 year of age in whom the diverticulum became acutely inflamed and was removed, the mortality was 100 per cent. The mortality in the group with ulcer was 30 per cent.

SUMMARY

We have reported an apparently unique case of Meckel's diverticulum in which the mucosal surface near the tip was the site of a nonulcerated pedunculated adenoma composed of gastric and duodenal glands.

Table 4. Some Cases of Bleeding from Invagination of Meckel's Diverticulum With or Without an Associated Intussusception

Author	Year	Age Years	Sex	Comments	Result
We C and Franks	1878	1½	F	Bloody stools; diffuse colon bacillus peritonitis; invagination of diverticulum with an ileal intussusception; reduction; resection of intussusception and diverticulum	Died
and Mackenzie	1878	2½	F	Bleeding by rectum; invagination of diverticulum with intussusception of terminal ileum	Died
Brunner Case 2	1878	4	M	Blood in stools; abdominal pain; vomiting; accessory pancreas at tip of invaginated diverticulum; ileocecal intussusception; resection	Recovery
Robinson	1878	5	M	Abdominal pain; distention; a little blood in enema; enteric intussusception 4 inches long, with invaginated diverticulum; intussusception reduced, diverticulum excised	Died
Erdmann, Case 2	1900	9	M	Blood in stool; ileal intussusception with invaginated diverticulum at apex; resection	Died
Morrison	1901	5	M	Bleeding by rectum; invagination of diverticulum with ileal intussusception; excision of diverticulum	Recovery
Wainwright	1902	17	M	Bleeding by rectum; invagination of diverticulum with intussusception of ileum; reduction; excision of diverticulum	Recovery
Dobson	1903	4½	M	Pain; vomiting; blood and mucus by rectum; ileocecal intussusception with invaginated diverticulum at apex; resection	Recovery
Terry	1903	12	M	Blood in stool; ileal intussusception with invaginated diverticulum at apex; reduction; excision of diverticulum	Recovery
Zum Busch	1903	21	M	Bloody stools; invaginated diverticulum at apex of ileocecal intussusception; subserous lipoma at tip of the diverticulum; resection	Recovery
Bousquet	1901	30	M	History of attacks of abdominal pain and blood in stool; palpable mass in right lower quadrant in last three attacks; ileocecal intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Blze	1904	6	F	Bleeding by rectum; pancreatic tissue at tip of diverticulum which was invaginated and produced an ileocecal intussusception; reduction; resection of diverticulum and adjacent loop of intestine	Died
Richter Case 2	1906	8	M	Abdominal pain; bloody mucus by rectum later; ileocecal intussusception with diverticulum at apex; reduction; excision of diverticulum	Died
Coffey	1907	7	M	History of blood by rectum; ileocolic intussusception with invaginated diverticulum at hepatic flexure; resection	Recovery
Bidwell	1907	3½	M	Bleeding by rectum; intussusception-reduction; recurrence of symptoms; invaginated diverticulum at apex of ileal intussusception; resection	Recovery
Kothe Case 1	1908	23	M	History of abdominal pain, vomiting, no bowel movement; bloody stool following rectal examination after induction of spinal anesthesia; ileocecal intussusception with diverticulum at apex; resection; Murphy button	Recovery

Author	Year	Age, Years	Sex	Comments	Result
Kothe.............. Case 2	1908	7 mo.	M	Vomiting; distention; blood in enema return; small accessory pancreas at tip of invaginated diverticulum which formed the apex of an ileocolic intussusception; resection	Died
Gray..................	1908	8	M	Blood in stool; invaginated diverticulum at apex of ileocecal intussusception; partial reduction; resection	Died
Drummond............ Case 1	1912	5	M	Abdominal pain; bleeding by rectum; ileal intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Drummond............ Case 6	1912	29	M	Repeated attacks of pain in lower part of abdomen; large amount of blood by rectum with last attack; ileal intussusception with diverticulum at apex; resection	Died
Brennecke.............. Case 3	1913	5	M	Attacks of abdominal pains, vomiting, and bloody stools; ileal intussusception with diverticulum at apex	Recovery
Brennecke.............. Case 4	1913	9 mo.	M	Bloody stools; ileocecal intussusception with diverticulum and appendix in intussusceptum; resection	Died
Douriéz................	1922	18	M	Abdominal pain, vomiting; blood in stool once; invagination of diverticulum in ileum; resection	Died
Stone, E.	1923	1½	M	Bloody stools unmixed with mucus; gastric mucosa at tip of invaginated diverticulum; no intussusception; no ulcer of diverticulum found	Recovery
Schlutz.................	1926	3 mo.	Not stated	Slight bleeding by rectum; ileal intussusception containing a diverticulum, which was acutely inflamed and ulcerated; resection	Died
Montgomery..........	1928	2¼	F	Two bloody stools; ileal intussusception with diverticulum at apex; reduction; excision of portion of diverticulum	Died
Shanon............... Case 1	1928	4½ mo.	F	Frequent bloody stools; inverted diverticulum with an ileal intussusception; resection	Died
Doolin................	1929	44	M	Bleeding by rectum; ileocolic intussusception with perforated invaginated diverticulum at apex; resection of intussusception and diverticulum	Recovery
Christopher...........	1930	9 mo.	M	Bleeding by rectum; ileocecal intussusception with diverticulum at apex; reduction; diverticulum not excised	Died
Hudson and Koplik.... Case 5	1932	7 wk.	M	Blood in stool; ileocolic intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Hudson and Koplik.... Case 8	1932	10½	M	Bleeding by rectum; ileocolic intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Hudson and Koplik.... Case 9	1932	7⅔	F	Blood in stool; ileocolic intussusception with diverticulum at apex; reduction; excision of diverticulum; gastric mucosa in diverticulum	Recovery
Hudson and Koplik.... Case 21	1932	½	M	Blood by rectum; ileocecal intussusception with diverticulum at apex; reduction; excision of diverticulum; gastric mucosa in diverticulum	Died
Hudson and Koplik.... Case 22	1932	½	M	Bleeding by rectum; ileo-ileocolic intussusception with diverticulum at apex; reduction; diverticulostomy	Recovery
Hudson and Koplik.... Case 27	1932	3¾	M	Blood in stool; index ... ... of diverticul ... obstruct ... ina- tion of ... gas- tric mucosa present in diverticulum	Died
McCann..	1932	6	M	History of bleeding by rectum; constipation; pain in lower part of abdomen; invaginated diverticulum in lower part of ileum; excision; diverticulum lined with duodenal mucosa; pancreatic tissue found in muscle layer	Recovery

The case emphasizes that extremely severe acute symptoms including abdominal pain and bleeding from the rectum, unmixed with mucus, may occur in persons with Meckel's diverticulum without any evidence of invagination, intussusception or ulceration.

In this case, as in several previously reported (table 3), there was heterotopic tissue in the diverticulum, but the source of the bleeding could not be determined either at operation or microscopically. It is reasonable to suppose, however, that it must have come from the diverticulum, since hemorrhage did not recur after its removal (three years' follow-up).

Because our patient, together with others (table 3), exhibited symptoms similar to those recorded for the group who had bleeding associated with ulcer of a Meckel's diverticulum, we believe that the latter condition cannot be considered as a clinical entity.

Search for a Meckel's diverticulum should always be made when there is unexplained bleeding by rectum or peritonitis of undetermined origin, or when the operative findings are not in accord with the clinical diagnosis. The indication is to remove the diverticulum even though it may appear harmless, because the mortality is high after perforation or after acute pathologic processes set in. The mortality in thirty-five cases of perforated ulcer of Meckel's diverticulum was 42.5 per cent.

A person with a lesion of Meckel's diverticulum, especially if the lesion is bleeding peptic ulcer, may pass from a state of relatively good health to one of acute illness, collapse and shock with amazing rapidity. Sudden severe pain in the lower part of the abdomen with rigidity, signs of diffusing peritonitis, fever and leukocytosis, especially in children, should lead one to suspect a perforated Meckel's diverticulum.

Cryptic intestinal bleeding should always constrain one to suspect a Meckel's diverticulum as a possible source.

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PEPTIC ULCER

IX. CHRONIC LESIONS OF THE DUODENUM FOLLOWING EXPERI-
MENTALLY PRODUCED PYLORIC DYSFUNCTION

CHARLES BRUCE MORTON, M.D.

Assistant Professor of Surgery and Gynecology, University of Virginia

UNIVERSITY, VA.

Some demonstrable and appreciable dysfunction of the pylorus is often found in patients who have peptic ulcer, whether the ulcer is situated in the stomach or in the duodenum. The dysfunction is not a passive stenosis but an active disturbance of the normal rhythm of the pylorus. Roentgenologically and at the time of operation, various degrees of spasm, hypertonicity and occasionally even slight hypertrophy have been demonstrated so frequently that they are generally accepted as phenomena almost concomitant with peptic ulcer. For this reason atropine, which tends to relax the pylorus, has been used for a long time in the medical management of patients with peptic ulcer and not infrequently seems to be a real factor in the amelioration of symptoms and the control of certain forms of the disease.

Two conflicting theories concerning dysfunction of the pylorus in cases of peptic ulcer have been advanced. One is that the dysfunction is secondary, the result of the ulceration. The other hypothesis is that pyloric dysfunction in such cases is primary and therefore may have some bearing on the etiology of peptic ulcer.

Accordingly, the following procedures were devised to produce experimentally in dogs a pyloric dysfunction that might be studied to investigate the possible relationship between abnormal function of the pylorus and the formation of peptic ulcer. The animals were studied roentgenologically and by exploratory operation or necropsy at various intervals up to two years after the induction of pyloric dysfunction. The results are described in this report.

METHOD OF EXPERIMENTATION

The principle of the experimental method devised was the addition of what might be termed an accessory pylorus at the outlet of the stomach. This was accomplished by the transplantation of a segment of jejunal muscle with intact mesentery to encircle the otherwise normal and undisturbed pylorus. It was thought that an independently contractile ring of muscle might interfere with the normal rhythm of the pylorus and thereby cause pyloric dysfunction.

Normal healthy dogs were used in all experiments, and for all operative procedures ether anesthesia and an aseptic technic were employed. No rubber-covered or other intestinal clamps and no unabsorbable sutures were used in any of the operations.

Through an upper midline incision the pylorus was exposed. By blunt dissection small openings in the gastrohepatic and the great omentum (there is no gastrocolic omentum in the dog) were made at the pyloric ring. These were made to permit the passage of a tape for traction and later a ring of transplanted muscle
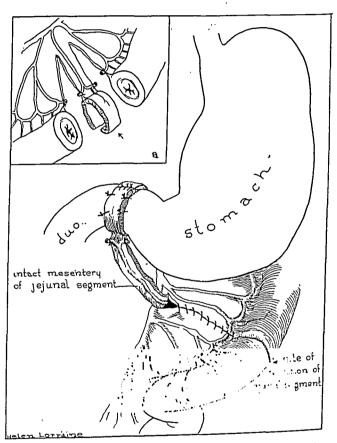
Fig. 1.—Diagram of operation for placing around the pyloric ring a segment of jejunal muscle with intact mesentery; *a,* method of preparing the segment of jejunum by resection, antimesenteric section and excision of the mucosa.

completely around the pyloric ring, in contact with its serosal surface and without interfering with the blood vessels and nerve connections in the region.

The jejunum, beginning at the ligament of Treitz, was examined until a segment with the desired characteristics was found. This segment, from 2 to 3 cm. in length, was supplied by a branch of the mesenteric vessels long enough to permit the approximation of the segment of intestine and the pylorus without tension at the direct enough to permit the resection of the segment with intact mesenteric vascular and nerve connections. This segment was resected and the severed end

of the jejunum adjacent to it were united by end-to-end anastomosis, thereby restoring the continuity of the gastro-intestinal tract.

The isolated, ringlike segment of jejunum with its mesenteric attachment intact was sectioned opposite the mesentery and its mucosa peeled away in a sheet, leaving a strip of muscle with independent circulation (fig. 1 *a*). The tape previously placed around the pylorus was used for traction and exposure, and an Allis forceps was passed behind the pylorus; one end of the strip of muscle was grasped by it and half of the strip pulled through. The tape was then withdrawn and the other half of the strip of muscle was folded over the anterior surface of the pylorus, and the two ends of the muscle were sutured together. The resulting ring of muscle was adjusted and held in place, immediately surrounding and overlying the pyloric ring, by a few interrupted sutures of fine catgut (fig. 1).

In the animals subjected to this operation a ringlike segment of jejunal muscle with intact mesenteric blood and nerve supply surrounded the pyloric ring throughout its entire circumference. Any independent contraction of the jejunal ring tended to close the pyloric orifice of the stomach in the same manner that contraction of the pyloric ring closed the orifice. Synchronous actions of the two rings were complementary, while asynchronous actions were in opposition to each other. In either instance the normal action and function of the pylorus were disturbed.

RESULTS

The operative mortality was not high, only one dog in eight succumbing to the immediate operative procedure. The state of nutrition and the general condition of the animals did not seem to be altered in any way, there being no loss of weight and no anorexia or weakness, even in the dog surviving for two years. During the course of the experiment one animal gave birth to and reared a litter of puppies uneventfully. No complications were observed except in two instances in which apparently some mucosal cells, which must have been incompletely stripped from the transplanted band of muscle, proliferated and formed a small cyst, filled with a cheesy material similar to that found in sebaceous cysts in man. It was interesting to see the apparent normality of the mucosa lining these cysts, even to the reproduction of intestinal glands.

Anatomic and Physiologic Observations.—Exploratory operations on the animals demonstrated that the transplanted ring of jejunal muscle had healed in place so well that it resembled a part of the pyloric ring itself. It had become "peritonealized" smoothly and appeared to be healthy. It seemed to derive part of its circulation from its original mesenteric vessels and part from the pyloric circulation with which it seemed to have anastomosed itself. Its mesentery had resolved itself into a "peritonealized" cylindric cord, in which the arterial pulsations were plainly visible and palpable. Microscopic examination of this cord revealed apparently normal vascular channels (fig. 2).

The jejunal ring was seen to contract frequently of its own accord. Also local stimulation of the ring itself or of its mesentery caused con-

traction of the muscle. When the muscle contracted there was a definite constricting action on the pylorus. It was noted, however, that the pyloric ring was relatively so much stronger than the jejunal ring that the latter could not seriously interfere with strong contractions of the pyloric muscle itself. Electrical stimulation of the wall of the intestinal ring caused violent contraction of the circular muscle fibers, while electrical stimulation of the mesentery caused contraction of the longitudinal muscle fibers of the intestinal ring.
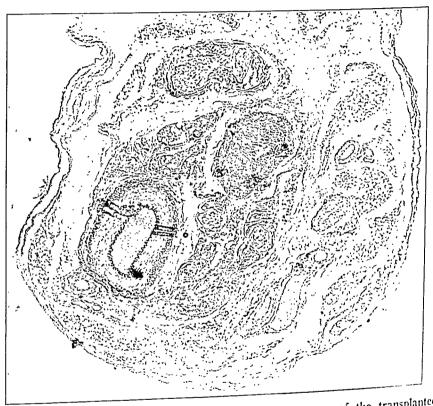
Fig. 2.—Photomicrograph of a section of the mesentery of the transplanted ring of the jejunum, with normal vessels; × 50.

Roentgenologic Observations.—The technic of the examinations was essentially the same as that described by me [1a] in a former report except that the contrast medium was a commercially supplied barium-cereal mixture. The dogs ate the meal readily, and it was satisfactory in every respect. Both fluoroscopic and roentgenographic examinations were made.

1a. Morton, C. B.: Observations on Peptic Ulcer: II. A Roentgenologic Study of Experimental Chronic Ulcer, Ann. Surg. 85:222, 1927; V. Findings in Experimentally Produced Peptic Ulcer; Etiologic and Therapeutic Considerations, ibid. 87:401 (March) 1928.

The observations on the animals of the experiment were controlled by similar observations on the same animals preoperatively and on other normal animals on which no operation had been performed. In the normal dog the stomach emptied with a certain degree of regularity and rhythm until it was completely empty in from three to four hours.

In the animals with a transplanted jejunal ring around the pylorus, however, the emptying was much less regular and rhythmic. The stomach appeared somewhat dilated and more bulbous than normal. In all instances the pylorus seemed to offer a definite resistance to rhythmic
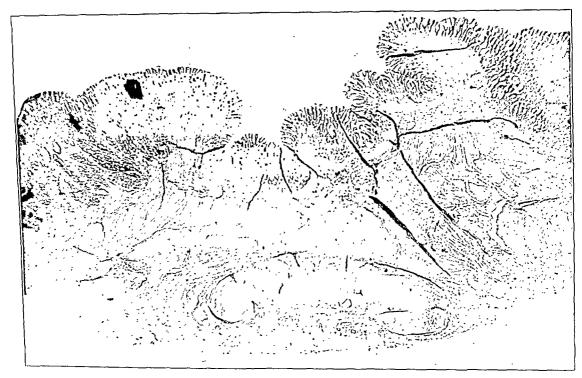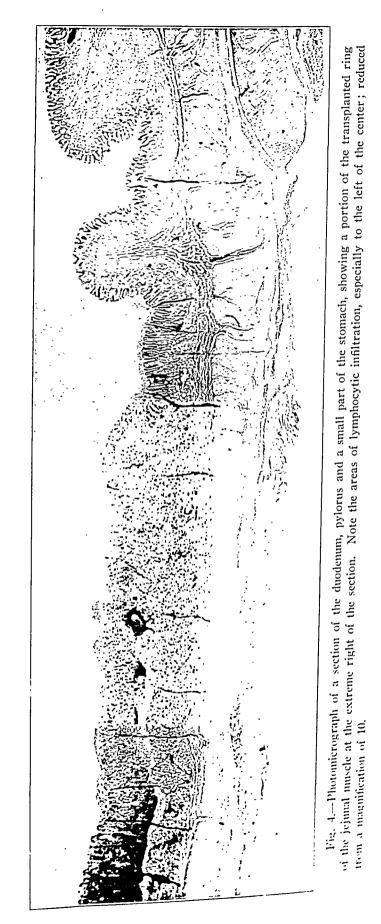
Fig. 3.—Photomicrograph of a section through the pylorus showing the transplanted ring of jejunal muscle; reduced from a magnification of 10. Note the definite evidence of duodenitis to the left of the pylorus.

emptying of the stomach. At the end of four hours there was an appreciable residue of the contrast medium in the stomach. No ulcerations of the duodenum or stomach were demonstrated. In general, the roentgenologic characteristics of the animals of the experiments were somewhat similar to the roentgenologic abnormalities found in patients with pylorospasm and other similar pyloric dysfunctions.

General Observations.—No gross ulceration of the duodenum or stomach was found in any experiment but in every one of them there

Fig. 4.—Photomicrograph of a section of the duodenum, pylorus and a small part of the stomach, showing a portion of the transplanted ring of the jejunal muscle at the extreme right of the section. Note the areas of lymphocytic infiltration, especially to the left of the center; reduced from a magnification of 10.

was gross and microscopic evidence of duodenitis (table). In an equal number of dogs used as controls no evidence of duodenitis was discovered. Some of the controls were normal animals on which no operation had been performed; others had had an abdominal incision with handling of the stomach and duodenum and others had undergone operations on the biliary tract in the course of other experiments.

The gross evidence of duodenitis in the animals of the experiments was not marked. No apparent serosal stippling and no marked thickening of the wall of the duodenum were seen. Inside the lumen, however, the mucosa frequently had a slightly eroded and definitely reddened appearance.

Data of Seven Experimental and Seven Control Animals

Dog	Operation	Date of Operation	Observation, Date	Results, Gross and Microscopic	Duration of Experiment
1	Jejunal band around pylorus	Jan. 14, 1930	Exploration, Jan. 16, 1933	No ulcer Duodenitis	2 years
2	Jejunal band around pylorus	Oct. 31, 1929	Exploration, Jan. 31, 1930	No ulcer	3 months
			Necropsy, May 30, 1930	Duodenitis	7 months
3	Jejunal band around pylorus	Oct. 29, 1929	Exploration, Jan. 31, 1930	No ulcer	3 months
			Necropsy, Feb. 13, 1930	Duodenitis and gastritis	3½ months
4	Jejunal band around pylorus	June 19, 1930	Necropsy, Feb. 26, 1931	Duodenitis	8 months
5	Jujenal band around pylorus	June 18, 1930	Necropsy, Feb. 26, 1931	Duodenitis	8 months
6	Jejunal band around pylorus	June 20, 1930	Necropsy, Feb. 26, 1931	Duodenitis	8 months
7	Jejunal band around pylorus	April 9, 1931	Necropsy, June 22, 1932	Duodenitis	14½ months
Seven control animals	Undisturbed gastro-intestinal tract	Tissue examined grossly and microscopically		Normal duodenum and stomach	

Microscopic examination of the tissue revealed changes similar to those characteristic of duodenitis in man. These consisted of various degrees of superficial mucosal erosions, infiltration of the mucosa and submucosa with lymphocytes, polymorphonuclear leukocytes and plasma cells, congestion of the capillaries, slight edema and fibrosis, evidence of apparently increased glandular epithelial activity and, last but most striking, various-sized collections of lymphocytes (figs. 3, 4, 5 and 6). The degree of duodenitis varied in proportion to the duration of the experiment. Lymph follicles, which are found normally in the duodenum of the dog, were seen in sections of the duodenum of the normal control animals. These follicles, however, were different from the collections of lymphocytes found in the duodenum of the animals of the experiments.

COMMENT

Judd and Nagel [1b] and Kirklin [2] have described the clinical features of duodenitis. The relationship of duodenitis and gastritis to duodenal and gastric ulcer has been thorougly studied by Wellbrock,[3] who cited
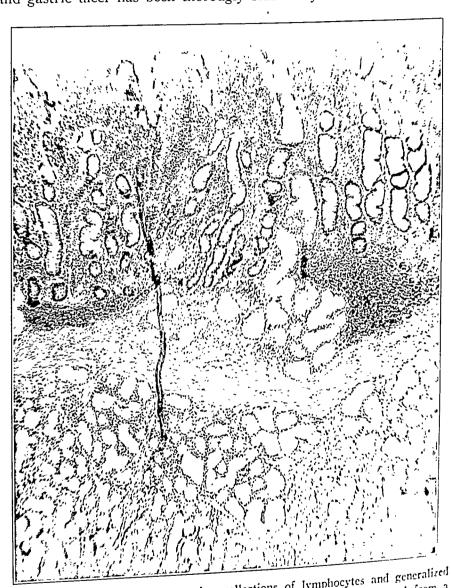

Fig. 5.—Photomicrograph showing collections of lymphocytes and generalized lymphocytic infiltration of the tissue in an area of duodenitis; reduced from a magnification of 75.

1b. Judd, E. S., and Nagel, G. W.: Duodenitis, Ann. Surg. 85:389 (March) 1927.

2. Kirklin, B. R.: A Roentgenologic Consideration of Duodenitis, Radiol' 12:377 (May) 1929.

3. Wellbrock, W. L. A.: Duodenitis and Duodenal Ulcer, Ann. Surg. 91:5 (April) 1930.

also similar considerations by Hauser,[4] Konjetzny,[5] and Konjetzny and Puhl.[6] As stated by Wellbrock, in many cases of duodenal ulcer in which clinical symptoms and roentgenograms are indicative of ulcer, a definite ulceration cannot be found at operation. Instead duodenitis is demonstrated. It is described as occurring in various forms, as simple duodenitis, duodenitis with erosion and ulceration, chronic duodenitis and healed ulcerated duodenitis. There are lymphocytes, polymorphonuclear leukocytes, plasma cells and a few eosinophils with congestion of the capillaries in the mucosa of the duodenum. In the more advanced chronic types the inflammatory reaction manifests itself by distinct hyperplasia of Brunner's glands, with infiltration of scattered lymphocytes and collections of lymphocytes throughout. The muscularis propria also contains some fibrous connective tissue. The blood vessels are sclerosed, the sclerosis increasing with the chronicity of the condition. The frequent association of the aforementioned changes characteristic of duodenitis with duodenal ulcer suggests a definite relationship between the two, duodenitis in all probability frequently preceding the formation of a peptic ulcer.

Comparison of the microscopic characteristics of duodenitis in man with the microscopic changes in the duodenum of the animals of the experiments demonstrates a close similarity between them. Analysis of the conditions of the experiments indicates several features that should be stressed.

The experiments were made in the dog, an animal in which spontaneous peptic ulcer occurs only with extreme infrequency. Acute ulcerations made experimentally in dogs heal with great rapidity. Chronic ulcerations have not been made experimentally in dogs with any consistency except by procedures which divert the alkaline juices in the duodenum away from that portion of the intestine into which the stomach empties, as for instance in experiments with surgical duodenal drainage.

Furthermore, the experimental procedures apparently affected directly only one very limited part of the gastro-intestinal tract, the pylorus. But the importance of that small ring of muscle may be more thoroughly appreciated when one considers the control which it must

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4. Hauser, G.: Ueber die Beziehungen der chronischen Gastritis und Duodenitis zum chronischen Magen-und Duodenalgeschwür, Med. Klin. **23**:120 (Jan.) 1927.

5. Konjetzny, G. E.: Entzündliche Genese des Magen-Duodenalgeschwürs: Ein Beitrag zur Kenntnis der Aetiologie, Pathogenese und Therapie des Magen-Duodenalgeschwürs, Arch. f. Verdauungskr. **36**:189, 1925.

6. Konjetzny, G. E., and Puhl, H.: Ueber die Bedeutung der Gastritis und Duodenitis für die Entstehung des Magen-und Duodenalgeschwürs, Med. Klin. **23**:986, 1927.

exert over the emptying of the stomach, the regurgitation of material from the duodenum into the stomach and hence neutralization of the acid gastric chyme by the alkaline duodenal juices.

The experimentally produced alteration in the function of the pylorus was not the production of a rigid unyielding stenosis, such as

Fig. 6.—Photomicrograph of a collection of lymphocytes and other cells in an area of duodenitis; reduced from a magnification of 250.

might be caused by placing a rigid band around the pylorus. Rather, the experiment produced an altered function by interfering with the rhythm of the pylorus or getting it "out of step." It did not prevent complete opening of the pylorus, nor did it prevent complete closure.

but it prevented the opening and closing of the pylorus as it would normally open and close in response to the usual stimuli. The interference was demonstrated both by direct observation and by roentgenologic examination.

It could be seen that the abnormal pyloric function interfered with emptying of the stomach, and therefore it seems fair to assume that it interfered likewise with regurgitation and hence with orderly neutralization of the acid gastric chyme. Had the transplanted band of contractile muscle been able to exert a force equal to that of the powerful pyloric ring, more profound alteration in pyloric function might have ensued.

The demonstrable pyloric dysfunction of the experiments was followed by the formation of a chronic inflammatory lesion of the duodenum which, though not an actual peptic ulceration, is generally considered a closely related pathologic change. If one assumes that the altered pyloric function interfered with normal neutralization of the acid gastric chyme by the alkaline juices in the duodenum, one has a factor similar to, though of course not so potent as, that which with great consistency causes chronic peptic ulcers following the diversion of the alkaline juices by surgical duodenal drainage. Mann and Williamson[7] and I[8] have reported various experiments of this character.

In a series of cases previously reported by me,[9] simultaneous analyses of the contents of the stomach and duodenum were made in normal persons and in patients with peptic ulcer. The results indicated appreciably less complete prepyloric and postpyloric neutralization of the acid chyme in patients with peptic ulcer than in normal persons. This variation seemed most probably due to a difference in the action of the pylorus in the two groups.

The importance of the pylorus in relation to duodenitis and duodenal ulcer has been demonstrated clinically by Judd and Nagel, Horsley[10] and Martin and Burden.[11] They have shown that resection of a portion of the pyloric muscle is a satisfactory and effectual means of bringing about healing of both duodenitis and duodenal ulcer.

7. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

8. Morton, C. B.: Observations on Peptic Ulcer: II. A Roentgenologic Study of Experimental Chronic Ulcer, Ann. Surg. **85**:222, 1927; V. Findings in Experimentally Produced Peptic Ulcer: Etiologic and Therapeutic Considerations, ibid. **87**:401 (March) 1928.

9. Morton, C. B.: Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis, Am. J. M. Sc. **177**:65 (Jan.) 1929.

10. Horsley, J. S.: A New Operation for Duodenal and Gastric Ulcer, J. A. M. A. **73**:575 (Aug. 23) 1919.

11. Martin, E., and Burden, V. G.: Pyloric Achalasia and Peptic Ulcer, Ann. Surg. **88**:565 (Sept.) 1928.

CONCLUSIONS

In conclusion, the results of the experiments, in which a degree of alteration in the normal function of the pylorus was produced by encircling the pyloric ring with a contractile band of jejunal muscle, seem to indicate that primary pyloric dysfunction may cause chronic inflammatory lesions of the duodenum. In the dog the lesion is a duodenitis which is almost identical with duodenitis in man. Because of the definite relationship between duodenitis and duodenal ulcer clinically, the probable significance of the results as regards the etiology of peptic ulcer in man is at least suggestive.

SIGNIFICANCE OF ANAEROBIC ORGANISMS IN PERITONITIS DUE TO LIVER AUTOLYSIS

BACTERIAL FLORA OF THE LIVER AND MUSCLE OF NORMAL DOGS

HAROLD M. TRUSLER, M.D.

AND

JAMES R. REEVES, B.S.

INDIANAPOLIS

The recent investigations of Ellis and Dragstedt [1] have reopened the question of the bacterial flora of normal living tissue. They found a gram-positive anaerobic bacillus present in the liver of normal dogs and in the peritoneal exudate of dogs dying from intraperitoneal autolysis of fresh liver and sterile liver. Andrews and Hrdina,[2] while doing research work in connection with the same problem, found toxic strains of Clostridium welchii in the peritoneal exudate of dogs dying of liver peritonitis. They also refer to the liver organism as Bacillus welchii. The organism that these workers recovered produces a filtrate which, in large doses, is lethal for guinea-pigs and rabbits. Rewbridge [3] found B. welchii in the peritoneal exudate formed from injections of bile and bile salts and assumed it to be the agent in death from this cause.

The bacterial flora of killed animal tissue has been studied by many investigators, but the findings cannot be considered as typical of living animal tissue. Wolbach and Saiki [4] in 1909 studied the bacterial content of the livers of twenty-three living dogs. They found a gram-positive anaerobic spore-bearing bacillus present in twenty-one of twenty-three livers which was similar to, but not identical with, B. welchii. Reith [5] cultured the muscle and blood of living animals and found that of 108 samples from healthy dogs, rabbits and guinea-pigs, the muscular tissues were 83 per cent positive and the blood 84 per cent positive for bacteria

1. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis In Vivo, Arch. Surg. 20:8 (Jan.) 1930.

2. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. 52:61 (Jan.) 1931.

3. Rewbridge, A. G.: Etiological Rôle of Gas-Forming Bacilli in Experimental Bile Peritonitis, Surg., Gynec. & Obst. 52:205 (Feb.) 1931.

4. Wolbach, S. B., and Saiki, T. A.: A New Anaerobic Spore-Bearing Bacterium Commonly Present in the Livers of Healthy Dogs, J. M. Research 21:267, 1909.

5. Reith, A. F.: Bacteria in Muscular Tissues and Blood of Apparently Normal Animals, J. Bact. 12:367 (Nov.) 1926.

of various types. Berg, Zau and Jobling [6] found the animal liver to contain an anaerobe with the same characteristics as the organism described by Wolbach and Saiki, but found bile and blood to be uniformly sterile.

In view of some differences in results when the work of Andrews and Hrdina was repeated in this laboratory, we have attempted to ascertain if toxic strains of C. welchii regularly inhabit the liver of healthy dogs and if the same organisms are present and cause death in in vivo autolysis of liver. To this end we have studied the livers of sixteen normal healthy dogs and the muscle tissue from six dogs and present a preliminary paper on a cultural study of the organisms found.

METHOD OF OBTAINING SPECIMENS

Stock dogs were given injections of morphine and atropine one hour previous to the operation. The abdomen was shaved, scrubbed with soap and water, washed thoroughly with ether and painted with iodine. Ether was used for anesthesia; the dogs were well draped with sterile linen. The operation was started with the surgeon wearing two pairs of gloves. The skin of some of the first dogs operated on was cut with a knife, but all the cultures obtained in this manner were contaminated with Staphylococcus and Streptococcus. It was found that if the skin was opened with a hot wire cautery, cultures did not contain these organisms. The final technic was as follows: The skin and fascia were opened with the cautery, the muscle was split with the fingers to eliminate bleeding, and the peritoneum was grasped in four Allis clamps and pulled out of the wound before cutting. At this stage the operator's first gloves were removed as a final precaution, and the presenting lobe of the liver was grasped in a large Kocher clamp. A freshly sterilized knife or the cautery was used to remove a few grams of liver around the point of the clamp, and the specimen was dropped into the culture mediums. The cut surface of the liver was sewed with black silk, the omentum was pulled down and tied to the operative site and the dog was returned to the pen.

We have spent ten months in the study and cultivation of known pure cultures of the Clostridium group, in the preparation of suitable and differential culture mediums and in the selection of methods of growth. We have studied three known toxic strains of C. welchii, two strains of Clostridium tetani, one strain of Clostridium edematis maligni and one strain of Clostridium putrificum. We have used a strain of C. welchii as a control for every cultural method used in growing the organisms isolated from tissue.

CULTURAL METHODS

We have found that good growth of all anaerobic organisms studied may be had in veal infusion meat medium in open test tubes without the aid of petrolatum or paraffin. One pound of lean ground veal to each liter of distilled water is infused in an icebox for twenty-four hours. After heating at 55 degrees for one hour the meat is filtered out, pressed and placed to a depth of from 2 to 3 in. ?

6. Berg, B. N.; Zau, Z. D., and Jobling, J. W.: Bactericidal F... the Liver, Proc. Soc. Exper. Biol. & Med. **21**:433 (Feb) 1927.

(5 cm. to 7.6 cm.) in large test tubes or Erlenmeyer flasks which are put in the autoclave for one hour and a half at 15-pound pressure. The broth is enriched to 1 per cent with peptone and to 0.5 per cent with sodium chloride, boiled five minutes and filtered. The clear broth is then titrated to p_H 8.0 and is boiled again for ten minutes. It is filtered again, distributed into the tubes containing the meat and sterilized in an Arnold sterilizer for one hour and a half on three successive days. Freshly ground dog liver is treated in the same manner for cultivation of liver organisms. For the production of exotoxins, fresh dog blood serum previously filtered through a Berkefeld candle is added to the veal medium, up to 10 per cent. The ground meat medium furnishes sufficient anaerobiosis to give good growth of all organisms studied.

Deep agar colonies for isolation of organisms are obtained in 1 per cent veal infusion agar or 1 per cent liver infusion agar grown in Burri tubes as modified by Hall.[7]

Surface agar colonies are grown in tubes devised in this laboratory, on various modifications of 3 per cent liver and 3 per cent veal infusion agar. Rabbits' blood, dried ox blood, hemoglobin and various sugars were used as enriching agents. Sodium sulphite agar, as reported by Wilson and Blair,[8] was used for differentiation. C. welchii and the organisms isolated from the dog muscle have been found to grow abundantly in jars of pure carbon dioxide under pressure. Neither the organism from the liver nor any of the other anaerobes studied would grow in this way in pure culture.

A veal meat infusion medium was used for all initial cultures, for subcultures after heating and for all stock cultures. Spore-forming organisms will remain alive in tubes of this medium for months.

ROUTINE FOR CULTURING SPECIMENS

Tubes containing the fresh liver obtained at operation were incubated at 40 C. for twenty-four hours. Rapid growth and the formation of much gas always resulted. A subculture was made into the same medium and the original culture was heated in a water bath to 80 C. for fifteen minutes, in order to kill all vegetative forms. Heating invariably resulted in a rapid increase in gas production to the point that the cultures appeared to be boiling. Another subculture was made after heating, and both subcultures were incubated for another twenty-four hours. Dilutions of the growing, heated culture were made in ordinary dextrose broth and as few organisms as possible transferred to a Burri tube. These tubes were incubated and frequently observed; they were removed when colonies appeared. The colonies were studied morphologically and transferred again to the stock medium, from which surface agar inoculations were made.

All inoculations of differential mediums were made from previously heated cultures. All were repeatedly picked from colonies in the Burri tubes which were widely separated or from distinct colonies on surface agar.

Fermentation reactions were obtained in 1 per cent liver agar to which the various sugars and Andrade's indicator had been added

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7. Hall, I. C.: An Improved Technic in Burri's Method of Isolating Obligately Anaerobic Bacteria, Am. J. Pub. Health **20**:536 (May) 1930.

8. Wilson, W. J., and Blair, E. M. M'V.: The Application of Sulphite-Glucose-Iron Agar Medium to the Quantitative Estimation of B. Welchii and Other Reducing Bacteria in Water Supplies, J. Path. & Bact. **27**:119 (Jan.) 1924.

RESULTS

Using the technic described, we have studied the livers of sixteen normal dogs. All specimens weighed approximately 4 Gm. and were removed in each case from the left lobe adjacent to the gallbladder. All specimens yielded a thermophilic anaerobe which we describe as "dog liver organism 1." As shown by the morphology and cultural charac-

Morphologic and Cultural Observations

	Clostridium Welchii*	Dog Liver Organism 1	Dog Muscle Organism 1
Morphology	In liquid medium, uniform short fat rods with truncated ends growing singly and in pairs; in 10 to 14 hour cultures bacilli very short, becoming longer until 4 to 6 microns long, granular, with irregular broken outlines at 72 hours	In liquid medium, long and short bacilli, slender, curved or wavy; no constant size or shape; ends square; grow in masses and long chains; longer and more variable in shape than the Welch bacillus	Large bacilli uniform in size with rounded ends; no tendency to curved forms; uniformity of organisms more pronounced in surface agar colonies; bacilli larger than B. welchii
Staining	Constantly G+ in young liquid cultures; G— in old cultures with staining variations in a single organism; agar colonies variable even in young cultures	Variable from earliest culture; predominance of G— forms in all cultures; granular forms usually predominate in old cultures	Stain a deep dark blue with little tendency to G— forms when growing in colonies; G+ and G— forms seen with equal frequency in liquid cultures
Motility	Nonmotile; encapsulated	Nonmotile; no capsule	Nonmotile; no capsule
Pathogenicity	Intramuscularly in pigeons: 1 cc. toxin dil. 1:4, death, 12 hours; 1 cc. toxin dil. 1:6, death, 24 hours	Intramuscularly in pigeons (average size): 1 cc. toxin dil. 1:4 in sodium chloride, harmless; 1 cc. toxin undil., harmless	Intramuscularly in pigeons: 1 cc. toxin undil., harmless
	Intraperitoneally in guinea-pigs (medium size): 1 cc. toxin undil., death; 6 hours; 2 cc. toxin undil., death, 3 hours	Intraperitoneally in guinea-pig (medium size): 6 cc. toxin undil., harmless	Intraperitoneally in guinea-pig (medium size): 2 cc. toxin undil., no harm; 6 cc. toxin undil., no harm
	Intraperitoneally in dogs: 35 cc. of a whole broth culture filtered to remove meat particles, death in 72 hours	Intraperitoneally in dogs: 35 cc. whole broth culture, meat free, harmless	

* Cultural characteristics of C. welchii are included for purposes of comparison.

teristics which we record in detail, this organism is not C. welchii and does not closely resemble it.

On two occasions we have incubated large masses of dogs' liver, keeping the left lobes separate from the right. In these instances we have found anaerobes other than organism 1. The bacterial content of the left lobes when incubated in large masses is more profuse than the right. Clostridium sporogenes and organisms of the Clostridium group which more closely resemble the Welch bacillus were found in the left lobe. In every case, however, they differed in sugar fermentation and pathogenicity. These organisms regularly ferment mannitol, inulin,
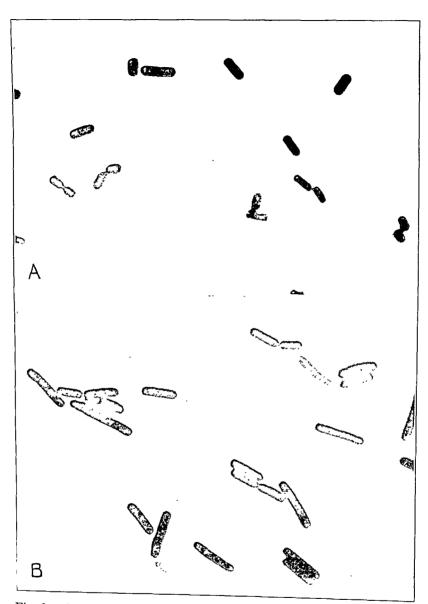
Fig. 1.—*A*, C. welchii in a twelve hour liquid culture in veal infusion meat medium; *B*, C. welchii in an eighteen hour surface colony on liver infusion blood agar under carbon dioxide.

glycerin, starch, sorbite and dulcitol. We were unable to demonstrate an exotoxin, nor were the organisms pathogenic when the whole organism was injected into a guinea-pig's muscle in young broth cultures.

Owing to our inability to insure strict bacteriologic technic in removing large masses of liver, we give no detailed descriptions of these occasional organsims. We strongly suspect that the bacterial flora of the dog's liver varies with different lobes, also varying in different animals and in the same animal at different times. However, the organism which we describe in detail as dog liver organism 1 has been found constantly present in the livers of sixteen normal dogs.

In studying dog muscle tissue, we have used a technic similar to that for liver. The skin was opened with a cautery, and 2 to 3 Gm. samples were taken. One sample of a dog's right rectus muscle was sterile; two samples of right rectus muscle and three other samples contained a strain of anaerobic bacilli differing from the liver organism and from C. welchii. A detailed description of this organism will be found in the table under the heading "Dog Muscle Organism 1."

C. Welchii on Veal Infusion Mediums.—Gas bubbles appear in from six to eight hours after the inoculation. The gas increases rapidly in amount until at the end of twenty-four hours the meat is infiltrated with gas and rises to the top of the liquid. The broth below is homogeneously clouded. Gas production becomes feeble after ninety-six hours, but occasional bubbles arise in this medium after standing for months at room temperature. There is no digestion of the meat, and the odor of these cultures is not unpleasant.

Organisms from Dog Liver on Veal Infusion Meat Mediums.—Gas bubbles in the subcultures do not appear for from seventy-two to ninety-six hours. Growth is then evident by a feeble production of gas which increases somewhat, but which never becomes rapid. The meat is never raised. Growth continues indefinitely; however, at the end of from seven to ten days the meat in the tubes is darkened and reduced to a mushy slime with a putrefactive and very offensive odor. The broth above the meat is at all times clear and is somewhat darkened.

Organisms from Dog Muscle on Veal Infusion Meat Mediums.— Gas appears in twenty-four hours and increases rapidly. The meat becomes infiltrated with the gas and rises to the top. The broth is milky. A fine white sediment accumulates in the bottom of the tube. Production of gas continues for forty-eight hours, and the meat falls to the bottom. At the end of six or seven days the meat is thoroughly digested and can be squeezed through fine cheesecloth. The cultures have a definitely putrefactive odor.

Colonies of C. welchii on surface agar usually appear to be raised. with an undulating surface and slightly irregular or crenated edges.

Fig. 2.—*A*, C. welchii in a thirty-six hour surface agar colony on heart infusion blood agar under illuminating gas; *B*, C. welchii in a seventy-two hour surface colony on sodium sulphite agar in an anaerobic tube.

They are opaque, moist and glistening. In deep agar, the colonies are round and white, solid at first, until after from eight to ten hours the presence of gas bubbles distorts the characteristic picture and colony formation is lost.

On surface agar, the liver organisms form flat, oval, scaly colonies with irregularly advancing edges. The surface is uneven and dry, and the colonies are yellow. In deep agar, the colonies appear as biconcave disks that are white with fuzzy outlines.

On surface agar, the colonies of the organisms found in muscle are rounded and droplike, with a moist, glistening surface. The surface is smooth. The edges are even and creamy yellow. In deep agar, the organisms grow diffusely through the medium.

Sodium Sulphite Agar.—C. welchii and other pathogenic anaerobes form black pigment on this medium. Grown in our anaerobic tubes, surface agar colonies of the Welch organism appear as black, shiny, raised dots in from eighteen to twenty-four hours. Deep agar and surface colonies of anaerobes from the dog's liver and muscle fail to form pigment at any time on this medium.

Sugar Fermentation.—Brown,[9] in a comprehensive study of anaerobic bacteria, has shown the variability of sugar fermentation even within a single strain. He concludes that anaerobes are divided into groups according to their ability to ferment sugars and according to their proteolytic powers, but that they cannot be rigidly divided as being either saccharolytic or proteolytic. We have found that C. welchii regularly ferments dextrose, sucrose, maltose and lactose with acid and gas, and that its proteolytic powers are very limited. Liver organisms have been found to ferment dextrose, lactose, starch, galactose and levulose, never sucrose and occasionally maltose. They have, however, the power of rapid proteolysis. Organisms from muscle form acid and gas in dextrose, lactose, maltose, inulin, starch, galactose, levulose, sucrose and mannitol. The proteolytic powers of these anaerobes are pronounced.

Pathogenicity.—In estimating the production of toxin of C. welchii the usual test methods were used. The cultures were made in veal infusion meat mediums to which fresh dog serum had been added up to 10 per cent. The toxin content was highest at forty-eight hours. Cultures were passed through a Berkefeld candle, and the resultant filtrate was tested by intramuscular injection into pigeons. Our cultures of C. welchii varied in toxicity, but all formed toxins to some degree, the highest testing 1:7 when diluted in physiologic solution of sodium chloride; that is, 1 cc. of a 1:7 dilution in physiologic solution of sodium

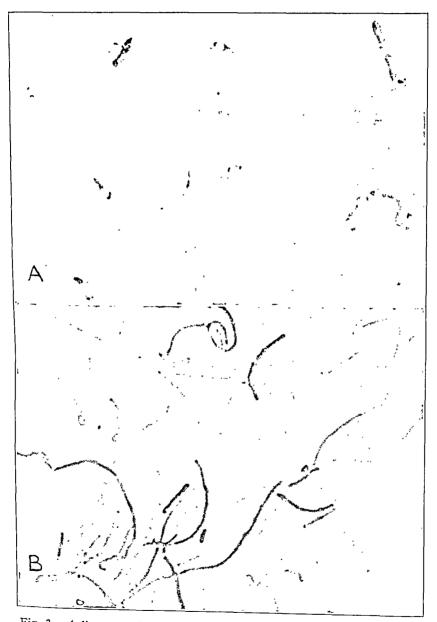9. Brown, J. H.: A Study of Anaerobic Bacteria, J. Bact. **10**:513 (Nov.) 1925.

Fig. 3.—*A*, liver organism in a twenty-four hour liquid culture in veal infusion meat medium (note the spores); *B*, liver organism in a fourteen day surface colony on 1 per cent dextrose liver agar in an anaerobic tube.
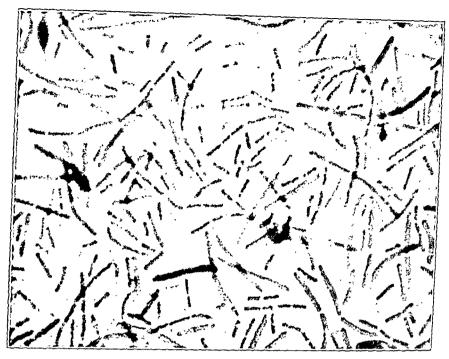
Fig. 4.—Liver organism in a seven day deep agar colony in 1 per cent dextrose, 1 per cent liver agar in Burri tube.
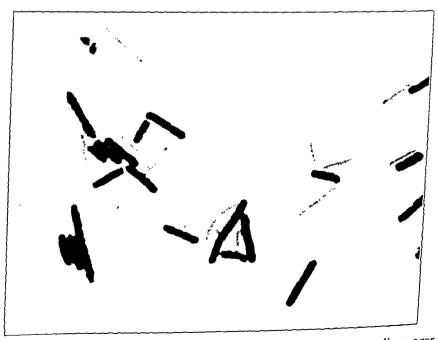

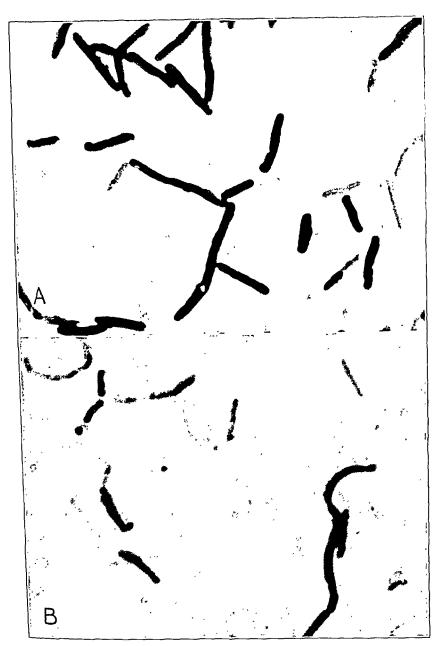Fig. 5.—Muscle organism in a thirty-six hour surface colony on liver agar under carbon dioxide.

Fig. 6.—*A*, muscle organism in an eighteen hour surface colony in dextrose heart infusion agar under carbon dioxide. *B*, muscle organism from a colony three months old on 1 per cent dextrose, 3 per cent liver agar in anaerobic tube (note the spore in the lower right corner).

chloride would cause death in twenty-four hours. Similar filtrates of organisms from liver and muscle were diluted and tested, and even in large doses of full strength we could demonstrate no harmful results. Rabbits, guinea-pigs and dogs were also used to test the material, which at no time gave toxic reactions.

COMMENT

The data included in this paper may serve to clarify much of the confusion concerning the gas-forming bacilli. It occurs to us that the term "gas bacillus" has been too loosely applied, and that it has been too commonly assumed that any gas-forming anaerobe is the Welch bacillus. We feel that this is true in previous reports on the cause of death in liver autolysis. We have not attempted to determine the exact identity of the liver or muscle organism; we have, however, used accepted cultural methods and strict bacteriologic technic to place these organisms within their proper metabolic group.

The organisms isolated from liver differ from those found in muscle in many respects. Organisms in muscle require less anaerobiosis, they form less gas, and they differ morphologically as well as in their reaction to heat. However, both types of organisms are spore-bearing anaerobes, they are nonmotile, they cause rapid digestion of meat with a strong putrefactive odor, and from the standpoint of exotoxin formation they are nonpathogenic. Organisms from both liver and muscle must occupy an entirely different place within the genus Clostridium than does the Welch bacillus. Damon and Feirer [10] described a group of thermophilic anaerobes which compare more closely to the organism isolated from dog liver than any that have been described. The organisms that we have isolated from liver differ from these thermophilic anaerobes only slightly in morphology and sugar fermentation. Muscle organisms do not compare with this group.

We do not insist that at all times we have been working with absolutely pure cultures. Our organisms were separated with care by means of picking off colonies and not by the single cell technic. We realize also that the number of specimens studied falls short of a quantity that would guarantee these organisms to be present in the livers of all normal dogs; with this in mind we are continuing to add specimens to this number as we study the rôle of anaerobic bacteria in death due to autolytic peritonitis, a report of which is to follow.

In two instances aerobic organisms were found in cultures from the liver, but were discarded without further study. It may be of interest to note that one of these organisms formed an intense red pigment in veal infusion mediums. It was also noted that the anaerobes present

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10. Damon, S. R., and Feirer, W. A.: Anaerobic Sporulating Thermophiles. J. Bact. **10**:37 (Jan.) 1925.

in the sixteen livers grew poorly in pure culture. The rapidity of growth and destruction of protein is markedly increased by symbiosis with Staphylococcus and B. coli.

As a result of studies so far made, we do not believe that toxic strains of C. welchii regularly inhabit liver or muscle of living dogs. We doubt the probability of its presence in tissues of a living dog. We agree that the livers of fetal dogs are sterile. The liver and muscle become the habitat of these organisms only after the first few months of life and after the ingestion of food. We attempt no explanation of their presence in the liver or in other tissue, but we do point out that they probably enter actively into the reduction of the body after death. Whether or not they enter actively into the process of disease remains to be determined.

CONCLUSIONS

1. Toxic strains of C. welchii were not found to be present in the livers of sixteen normal healthy dogs or in the muscles of six normal healthy dogs.

2. The livers of sixteen normal healthy dogs contained a strict anaerobic bacillus, thermophilic in its reaction to heat, a member of the genus Clostridium and of the metabolic group of nonsucrose-fermenting, putrefactive, gas-forming organisms.

3. The muscles of five normal healthy dogs contained a less strict anaerobic bacillus, not thermophilic in heat reaction, a member of the genus Clostridium and of the metabolic group of sucrose-fermenting, putrefactive, gas-forming organisms. A sample of muscle from one dog was sterile.

4. The organisms occupying the livers and muscles of the dogs studied do not produce an exotoxin. They are, in this respect, non-pathogenic.

5. These organisms are all large gram-positive bacilli. Their morphology and gas production easily confuse them with pathogenic forms.

6. On two occasions when large masses of liver were incubated, organisms were found which closely resembled C. welchii in morphology. They differ in sugar fermentation, form no exotoxin and were not pathogenic when injected in young broth cultures intramuscularly into guinea-pigs.

7. Livers of fetal dogs are uniformly sterile.

TUMORS OF THE PAROTID GLAND

IRVIN STEIN, M.D.

AND

CHARLES F. GESCHICKTER, M.D.

BALTIMORE

Whether considered from the clinical, pathologic or therapeutic standpoint, tumors of the parotid gland present problems difficult of solution. The benign neoplasms of this organ often show malignant tendencies in that they recur frequently after simple excision, whereas the malignant tumors often show benign features in that distant metastases rarely develop. Whether recurrence in a given case is a clinical feature of a benign process or a malignant feature of a type of carcinoma in which a tendency to widespread metastases is practically absent is not always easily decided. The composition of the majority of these new growths as seen through the microscope is likewise difficult of interpretation. Whether these tumors are truly mixed, with both connective tissue components and epithelial elements taking part in the neoplastic process, is by no means clear from a perusal of the literature. Authors differ in placing the responsibility for the new growth on the epithelium, the connective tissue, the myxoma or the cartilage found in these lesions, and the view that the entire process is endothelial is not without its adherents. From the standpoint of treatment, equally difficult decisions must be made. Since the continued growth of these tumors and manipulations for their removal both offer serious danger of damage to the adjacent facial nerve, the choice between surgical intervention and irradiation is often an extremely delicate one.

The many factors to be weighed in diagnosis, in pathologic interpretation and in treatment, as well as the fact that the occurrence of these tumors is by no means rare, lends importance to a thorough restudy of a large series of these cases.

The frequency of tumors of the parotid gland is indicated by previous publications on this subject, series of cases numbering over 50

(Wood [1] and Wilson and Willis [2]) and over 90 (Kennon,[3] McFarland,[4] Benedict and Meigs [5]) having been reported from various clinics. The following study of tumors of the parotid gland recorded in the surgical pathologic laboratory of the Johns Hopkins Hospital covers a period extending from 1888 to 1931 and includes a total of 241 cases. In most of these cases the records are complete and include both history and pathologic material. It has been possible to maintain close contact with the majority of these patients (145) for varying periods of time, and many of them have been followed from operation to the time of writing or until death. Infectious processes localizing in and affecting the parotid gland have not been included in this study, which is restricted to the neoplasms of the gland.

CLINICAL FEATURES OF PAROTID TUMORS

In a group of 50,000 patients surgically treated there were 241 parotid tumors (exclusive of those that were definitely submaxillary, sublingual or lacrimal), a ratio of 1 tumor to 208 persons. Of the 241 tumors, 42, or 17.4 per cent, were considered malignant after a study was completed of all data on which classification could be based. Parotid tumors may occur at any age, and in the present series ages are recorded from 8 to 80 years. Pailler [6] reported a tumor in a girl of 11 months; McFarland,[4] a tumor in a child less than 1 year of age, and Wood,[1] a rapidly growing tumor in a child of 7 months. Although there is a fairly wide age distribution, the majority of these tumors appear in persons between the ages of 20 and 45 years, with the highest incidence in the third decade. If the cases reported by McFarland and those he collected from the literature are added to the series of Benedict and Meigs [5] as well as to the series cited here, there is a total of 676 cases, of which 455 occurred in persons between the ages of 20 and 45 (fig. 1). A larger percentage of malignant tumors than of

1. Wood, F. C.: The Mixed Tumors of the Salivary Glands, Ann. Surg. **39**:57 and 207, 1904.

2. Wilson, L. B., and Willis, B. C.: The So-Called Mixed Tumors of the Salivary Gland, Am. J. M. Sc. **143**:656, 1912.

3. Kennon, R.: Tumours of the Salivary Gland, Brit. J. Surg. **9**:76 (July) 1921; **10**:85 (April) 1922.

4. McFarland, J.: Ninety Tumors of the Parotid Region, Am. J. M. Sc. **172**:804 (Dec.) 1926.

5. Benedict, E. B., and Meigs, J. V.: Tumors of the Parotid Gland, Surg., Gynec. & Obst. **51**:626 (Nov.) 1930.

6. Pailler, B.: Des épithéliomes polymorphes de le parotide, Thèse de Paris, 1903.

benign tumors occurred in persons over the age of 45, although the highest number of malignant tumors occurred in the third decade.

The incidence of these tumors is found to be greater in the white race (80.1 per cent) than in the Negro race (19.9 per cent). One case of carcinoma of the parotid occurred in a Chinaman. The two sexes were about equally affected. The tumors occur with practically equal frequency on both sides of the face, as follows:

	Right	Left
McFarland reports	28	38
McFarland reports from other sources	114	135
	225, or 47.2%	251, or 52.8%
Present series	70, or 52.6%	63, or 47.4%
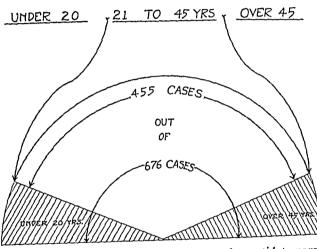
Fig. 1.—Chart showing age incidence of parotid tumors.

Concerning localization, the following statistics may be noted:

	Cases	Percentage
Angle of the jaw....................................	64	48.1
Over the parotid gland.............................	21	30.8
Submaxillary region	13	9.9
Mastoid region	8	6.0
Throat	7	5.2

The average duration of the benign mixed tumors of the parotid from the time a mass was first noticed to the time of operation was ninety-six months, or eight years. The average for the malignant form was fifty-one months, or slightly over four years. The symptoms in nearly one half of the cases of malignant tumors were of fifteen months' duration or less, whereas the duration of symptoms in only one eighth of the benign mixed tumors was within the same period. The shorter duration in the malignant form indicates definitely a more rapidly grow-

ing process. Such symptoms as pain, interference with hearing or sight and involvement of the seventh nerve occurred earlier in the malignant form and caused the patient to seek medical aid sooner than in the case of the benign tumor. This, as pointed out by McFarland,[4] is an aid in differential diagnosis between the benign and the malignant form.

Frequently a history was obtained of the presence of a nodule which was quiescent for as long as ten years, and which then manifested slow and progressive growth. In some cases this followed injury or infection, but most frequently no reason was found, and apparently neither trauma nor infection could be related definitely to the mixed tumors as a causative factor.

Delbet and Herrenschmidt[7] reported some cases following trauma. Kennon stated that a number of his patients gave a history of an injury
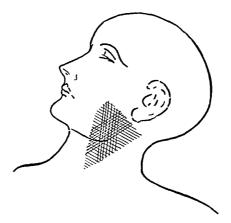
Fig. 2.—Chart showing the distribution of 241 parotid tumors.

to the area in which the tumor subsequently developed. In only 10 cases of the present series was there a history of trauma, and in but 14 a history of infection (mumps, influenza, sore throat or dental abscess) antecedent to tumor formation. It would thus appear that there is no definite evidence of any predisposing factors in the development of these tumors that can be obtained from the clinical history.

In the benign mixed tumors the most frequent symptom (fig. 3) was gradual growth with intervals of quiescence (even as long as ten years) usually followed by the slow and progressive enlargement so characteristic of these lesions. Rapid growth was rare, and when it occurred it was usually at the onset or just before operative intervention. Gradual growth occurred in 144 cases; rapid growth, in only 23.

Enlargement was rapid in 17 of the 42 malignant tumors, and in 7 the rate of growth varied a great deal during the course of the

7. Delbet and Herrenschmidt: Tumeur mixte de la parotide, Bull. Assoc. franç. p. l'étude du cancer 4:41, 1910.

disease. In 17 cases in the malignant group, the mass was evidently
adherent to some structure, either to the skin above or to the underlying
tissue; in 10 early cases it was adherent to the skin alone. When there
was an attachment to the structures below, the growth was always
adherent to the skin. Such adherence is the most constant clinical sign
of malignancy.

Local pain, rarely radiating to the scalp or to the upper half of
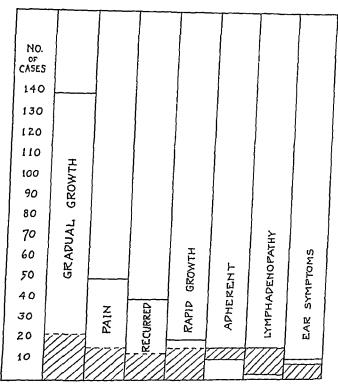the face, occurred in 37 of 151 benign lesions. The character of pain

Fig. 3.—Chart showing the symptoms and findings in benign (white area) and
malignant (crossed area) tumors of the parotid gland.

aids in the differentiation between the benign and the malignant form
of parotid tumors. In 15 cases of malignant tumor there was pain
of the radiating type. Although pain may occur in both the mixed and
the malignant tumors, in practically all of the benign growths there is
discomfort rather than pain, which is local rather than radiating.

In the entire series interference with chewing was noted three times,
apparently caused by mechanical interference of the growth with the
temporomandibular joint. Dysphagia was a rarer symptom, occurring
but two times; in each case the tumor occurred in the pharynx, the
explanation again probably resting on mechanical interference. Drain-
age of purulent material from the ear in otitis media, in association

with a tumor on the same side, was noted in 3 cases. Salivation was not observed in our series, though it has been described in the literature (Prengrueber [8]).

The benign tumors were of firm consistency, rubber-like, sharply circumscribed and not attached. The malignant tumors were usually more diffuse, more apt to be attached to the surrounding tissues and of a more variable consistency; they were at times harder and at times softer, but rarely of the same firmness as benign tumors. In 3 cases of the malignant group the tumor was noted to be rather soft in consistency and not at all circumscribed. In the other cases it was much firmer, and in a few cases it was quite discrete.
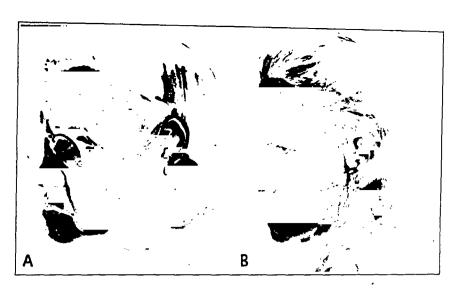
Enlargement of the cervical lymph nodes is another point of differentiation. In the malignant tumors this occurred in 13 of 42 cases, or in 30.9 per cent; whereas in the benign tumors it occurred in but 7 of 153 cases, or 4.5 per cent. The lymphatic involvement was unilateral in but 1 case of the malignant group and was bilateral in all the rest. It was confined to the cervical nodes in all the cases, with an exception in the benign group which was associated with a general enlargement of lymph nodes. In but 1 case was the swelling definitely proved to be caused by metastasis from the tumor. In others it was present when the patient presented himself for examination, but it could easily have been due to some infectious process, particularly about the upper respiratory tract. To support this view is the fact that in no case in this series was there other than a unilateral tumor, yet all cases of enlarged lymph glands save 1 were bilateral, and this case showed definite glandular enlargement after the onset of the tumor.[8a]

CLINICAL DISTINCTION BETWEEN BENIGN AND MALIGNANT TUMORS

Although the differentiation of benign from malignant tumors of the parotid gland is often an extremely difficult problem in the symptomatology and in the clinical examination, distinction between benign and malignant tumors can usually be made. Three of 4 benign tumors occur in the age period between 20 and 45 years, whereas 2 of 3 of the malignant tumors occur after 45 years and between the ages of 45 and 65. The duration of the benign tumors is twice that of the malignant, the former averaging eight years and the latter four years. Pain is mild and localized in the benign group, and is severe and radiating in the malignant group. The rate of growth is slow and gradual in one

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8. Prengrueber, cited by Ewing.[29]

8a. In only four cases among the malignant tumors of this series were metastases to distant organs verified. While the impression clinically is that a fair percentage of parotid cancers metastasize to the regional lymph nodes, such metastases are seldom verified microscopically, and are rarer than is generally supposed.
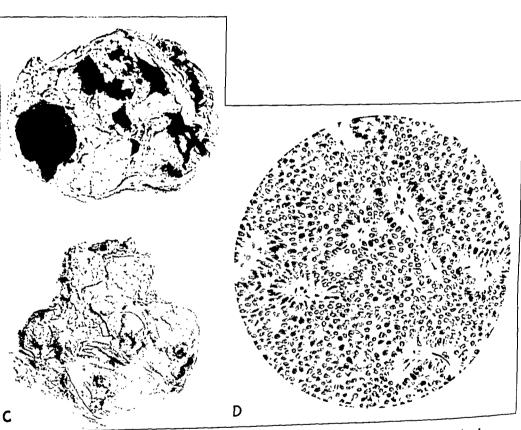
Fig. 4 (path. no. 21990).—Typical benign mixed tumor of the parotid gland. The patient was a white woman, aged 60, who had a tumor for twenty years at the angle of the left jaw. It grew gradually and progressively and became adherent below. There were no other symptoms. On Aug. 14, 1917, a complete excision of the tumor with the cautery was done. On Jan. 10, 1928, the patient died, ten and a half years after operation from other causes without evidence of recurrence. The pictures show:

A, side view emphasizing the lobulated character of the tumor.

B, postoperative result showing the scar and the drop of the lower part of the cheek. The facial nerve was severed in this case.

C, gross specimen. The upper illustration shows the cut surface; the lower, the capsule about the tumor. The cut surface is fibrillar and cystic. The outer surface shows the capsule enclosing the facial nerve.

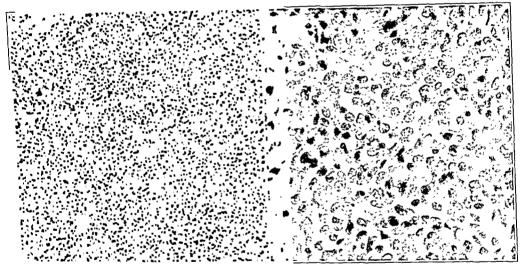D, photomicrograph showing the adenomatous character of the more cellular areas.

Fig. 5 (path. no. 26733).—Carcinoma of the parotid gland metastasizing to the cervical nodes and to the abdomen. Death occurred within two years. The patient was a white woman, 71 years old. She had a tumor for four years on the right side of the face at the angle of the jaw. It was about 2.5 cm. in diameter when first observed, but gradually and progressively grew and became adherent to the surrounding tissues and ulcerated on the crests. The patient lost much weight, and her cervical lymph nodes increased in size. The tumor was excised on Sept. 14, 1920; following operation she was better for a while; then there occurred bilateral metastases above the sternocleidomastoid muscles and later a mass in the abdomen. She died on Feb. 15, 1922, presumably from metastasis. The illustrations show:

A, patient before operation with a large ulcerating mass.
B, patient after operation with recurrence in the left cervical region.
C, low power photomicrograph showing diffuse grade III cancer.
D, high power photomicrograph showing malignant cuboidal cells.

group and more rapid in the other, the most rapid rate of growth being present in the more malignant lesions. On examination, a benign tumor of the parotid gland shows an encapsulated, firm, rubbery and nodular growth without enlargement of the regional lymph nodes. The malignant growth shows a more diffuse, adherent swelling which is either harder or softer than the benign lesion and which may be associated with an enlargement of the regional lymph nodes. These malignant tumors rarely ulcerate and fungate through the skin (figs. 4 and 5).
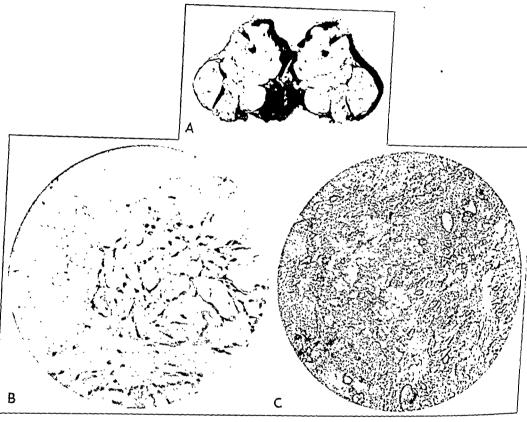

Fig. 6 (path. no. 23480).—Benign mixed tumor of the parotid with scanty and inconspicuous epithelial elements. The patient was a white woman, aged 31, who had a tumor behind the ear for ten years. It grew slowly and progressively, and there was local pain from the onset. A complete excision of the tumor was done on July 23, 1918. In 1919, the patient was well with no recurrence.

A, gross specimen showing the hyaline and cartilage-like areas visible on the cut surface.

B, photomicrograph showing the cartilaginous and precartilaginous stroma practically devoid of epithelial elements.

C, photomicrograph showing epithelial elements invading myxomatous areas.

PATHOLOGIC DISTINCTION BETWEEN BENIGN AND MALIGNANT TUMORS

In some cases in which the patient is middle aged with symptoms of several years' duration and the tumor is firm, but not definitely circumscribed, the distinction between benign mixed tumor and carcinoma of

the parotid cannot be made clinically. In other cases in the same age group with a similar duration of symptoms, the primary tumor may have been unsuccessfully excised elsewhere, and the recurrent growth may be even more difficult to diagnose. In such cases, particularly when tissue is already available for microscopic examination in a recurrent tumor, the pathologic changes may aid making the distinction.

The microscopic study shows a variation in cell structure with points of distinction between the more definitely benign groups, those with the greatest tendency to recur and those which terminate in death. The

Fig. 7 (path. no. 35501).—The patient was a white woman, aged 31, with a tumor of ten years' duration at the angle of the left jaw. Complete excision was performed in May, 1924, including a margin of normal parotid gland. A partial facial paralysis resulted. The photomicrograph shows the epithelial elements scattered among a large amount of fibrous and fibromyxomatous tissue in which many cystic spaces have formed.

most benign group has an adenomatous arrangement with a large amount of stroma in which myxomatous connective tissue and cartilage may be conspicuous features. The epithelial cells may be cuboidal, columnar or oval but are usually spindle-shaped and compressed by the abundant amount of stroma or matrix. These growths are referred to as mixed tumors of the parotid gland. Such typical mixed tumors are usually one of two microscopic types. In the first microscopic type, compressed basal cells arranged in thin strands pervade a lobulated and
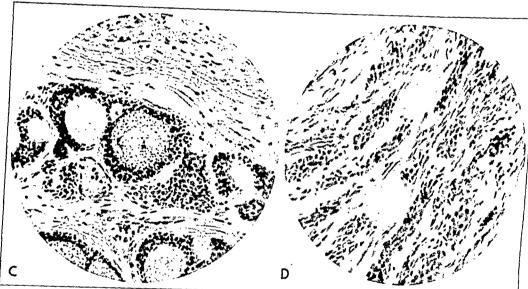
Fig. 8 (path. no. 23146).—Recurrent mixed tumor of the parotid. The patient was a white woman, aged 40, who had a tumor for three years which began just below the posterior zygoma and spread to the temporal region. It grew slowly. On May 8, 1918, it was excised piecemeal with the knife and the capsule broken. The tumor recurred a few months later. One year after this first operation radium treatments were begun and continued for eight months without improvement. In March, 1920, piecemeal excision with the cautery was done. The facial nerve was sacrificed. The cauterizations were done at repeated sittings. One year later, July 9, 1921, the patient was examined and found free from recurrence. The illustrations show:

A, patient after the first operation.

·B, patient after cauterization for recurrence.

C, high power photomicrograph from the recurrent specimen showing nests of basal cells invading the stroma. There is a definite adenocystic arrangement.

D, high power photomicrograph from the recurrent specimen showing the compressed basal cells intermingled with myxomatous fibrous tissue. In C and D, it can be seen that the tumor approaches adenocystic basal cell carcinoma in structure.

myxomatous matrix (fig. 6A and B). In the second microscopic type, the epithelial cell varies from a basal to a cuboidal or even to a squamous cell, and the stroma with numerous cystic spaces shows similar variations including hyalinized connective tissue, myxoma or cartilage (fig. 7). Microscopically, the most reliable index to the benign nature of these mixed tumors is the character of the stroma. The slower the rate of growth the larger is the amount of stroma and the more often is cartilage found.

In the recurrent tumor, areas of diffuse proliferation may be seen. The stroma is more predominantly fibrous than myxomatous, and the epithelial cells are more uniformly of the basal cell type. These cell
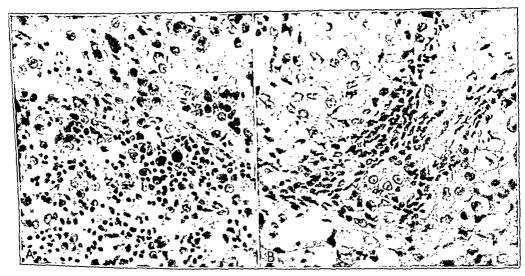

Fig. 9 (path. no. 9120).—Metastasizing carcinoma of the parotid gland. The patient was a white man, aged 45, with a gradual growth in the right parotid region of three and one-half years' duration. Enlargement of the lymph nodes appeared two months before death. Despite irradiation and tracheotomy, death occurred within less than four years after the initial operation.

A, diffuse invasion of the parotid gland by malignant epithelial cells.

B, structure of the tumor in a lymph node. Nests of large epithelial cells are seen.

groups may be arranged in an apparently adenocystic formation or in islands invading the stroma rather than in strands as seen in the mixed tumors (fig. 8). In the recurrent cases the microscopic picture overlaps that of so-called benign mixed tumors on the one hand and that of carcinomas on the other, since basal cell proliferation may predominate over the components of any of the three groups. Many of these recurrent tumors are basal cell carcinomas without a tendency to metastasize. Some of them are benign mixed tumors of the parotid with basal cell features which become more prominent after the first recurrence.

These tumors with basal cell features must be distinguished from a small group of malignant tumors of the parotid which are not related to the mixed or basal cell type but arise about the small ducts of the parotid and may produce diffuse islands of cuboidal cells or metastasize as cuboidal cell cancer (fig. 9). Another small group of malignant tumors composed of small spindle and round cells (fig. 5), described by Chevassu[9] as atypical carcinoma, approaches the basal cell cancer in structure. This is the type incorrectly described by Kuster,[10] Nasse,[11] Degen[12] and Schridde[13] as round cell sarcoma. These rare variants of cancer of the parotid are best referred to as atypical carcinoma after Chevassu.

Fig. 10 (path. no. 36754).—Recurrent basal cell cancer. The tumor, in a white woman, aged 42, was present nearly four years. It recurred twice and invaded the lymph nodes. Despite the last complete excision performed in June, 1925, there was recurrence with failing health in May, 1931. The photomicrograph of the basal cell cancer shows characteristic epithelial lobules with invasion of the fibrous stroma.

9. Chevassu, Maurice: Tumeurs de la gland sous-maxillaire, Rev. de chir. 41:145, 1910.

10. Kuster, F.: Arch. f. klin. Chir. 12:596, 1870.

11. Nasse, D.: Die Geschwülste der Speicheldrüsen und verwandte Tumorendes Kopfes, Arch. f. klin. Chir. 44:233, 1892.

12. Degen, W.: Ein doppelseitiges Sarkom der Parotis, Inaug. Dissert., Freiburg, 1900.

13. Schridde, H.: Ein Rundzellensarkom der Parotis, Beitr. z. path. Anat. u. z. allg. Path. 34:136, 1903.

When the patient is over 45 years of age, and when the tumor is adherent and rapidly growing, a neoplasm of the parotid may be expected to show basal cell features and to have a tendency to recur. A definite percentage of this group are true basal cell cancers (fig. 10). Only in rare instances will there be an atypical carcinoma (Chevassu) which has a tendency to metastasize. The firm nodular growths occurring in persons under the age of 45 with a longer duration of symptoms and a slower rate of growth usually will prove on microscopic examination to have mixed features with a large amount of myxomatous stroma and epithelial components containing benign cells arranged in thin strands or dilated acini. They will have less tendency to recur after treatment.

Thus there are pathologic factors leading to recurrence after treatment of tumors of the parotid. The recurrent tumor is most often a basal cell carcinoma or a benign mixed tumor with basal cell features. The microscopic distinction between the two is associated with clinical points of differentiation, as has been pointed out.

THE NATURE OF MIXED TUMORS

Difficulties in the histogenesis of parotid tumors have hinged about both the epithelial and the connective tissue components of the neoplasm. Although Kaufmann and Volkmann tried to derive these lesions from endothelium, it is now generally conceded that the more cellular areas are epithelial. The more difficult problem has been to account for the myxomatous and cartilaginous features found in the stroma. Krompecher,[14] Clementz [15] and others have thought that metaplasia or mucoid regression might account for the cartilaginous material as a product of the epithelial cells in the tumor.

These tumors were first described by Kaltschmied [16] in 1752. They were regarded as epithelial by Virchow [17] even though he pointed out the probable derivation of cartilage from connective tissue by metaplasia. Cohnheim [18] particularly was an adherent of the epithelial theory of the origin of these tumors.

This opinion persisted until Kaufmann [19] attempted to prove a relationship to endothelial structures on the basis of peritheliomatous

14. Krompecher, E.: Zur Histogenese und Morphologie der Mischageschwülste der Haut, sowie der Speichel- und Schleimdrüsen, Beitr. z. path. Anat. u. z. allg. Path. **44**:51, 1908.

15. Clementz, H.: Ueber das Schleimgewebe in Parotisgeschwülsten, Inaug. Dissert., Bonn, 1882.

16. Kaltschmied, C. F.: Tumore scirrhoso trium cum quadrante librarum glandulae parotids extirpato, Vienna, lit. Tennemannianis, 1752.

17. Virchow: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863-1867.

18. Cohnheim: Virchows Arch. f. path. Anat. **68**:547, 1876.

19. Kaufmann, C.: Das Parotis-Sarkom pathologisch-anatomisch und klinisch bearbeitet, Arch. f. klin. Chir. **26**:672, 1881.

and sarcomatous-like features. Then, Wartmann[20] in 1879, because of the polyhedral cells so frequent in the histologic structure of these tumors, maintained that they were derived from lymphatic endothelium. There appeared to be some truth in this contention, for these cells are small and polyhedral, and assume a flat or spindle form under pressure. Often they are adherent to the supporting connective tissue and appear to merge with it in a manner certainly suggesting an endothelial nature.

These observations so influenced Volkmann[21] that in 1895 he made a comprehensive study of the subject. He pointed out to what degree these tumors may simulate endothelial structures, and turned the tide of thought in the direction of the endothelial theory. For some time case reports were published under the heading of "Endothelioma of the Parotid."

The swing of opinion back to the epithelial theory of origin started in 1899 with Hinsberg,[22] who was supported by Ribbert[23] and later by Borrmann[24] in 1901. These men, by careful investigation and study of various cases, so adversely criticized the endothelial theory that there was a reversion of thought to the earlier views of Cohnheim.

In France, opinion had always been in favor of the epithelial origin, and though there was some dissension (Curtis and Phocas[25]) the theory was earnestly upheld by Collet[26] in 1896, Pitancé[27] in 1897, and Cunéo and Veau[28] in 1900.

In 1912, Weishaupt[29] and later Moral[30] agreed on the idea that the ramus of the mandible might furnish the peculiar embryonal material

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20. Wartmann: Untersuchungen über der Enchondrom, Inaug. Dissert., Strassburg, 1880.

21. Volkmann, R.: Ueber endotheliale Geschwülste, zugleich ein Beitrag zu den Speicheldrüsen-und Gaumentumoren, Deutsche Ztschr. f. Chir. **41**:1, 1895.

22. Hinsberg, V.: Beiträge zur Entwicklungsgeschichte und Natur der Mundspeicheldrüsengeschwülste, Deutsche Ztschr. f. Chir. **51**:281, 1899.

23. Ribbert, M. W. H.: Geschwulstlehre für Aerzte und Studierende, Bonn, F. Cohn, 1904, p. 385.

24. Borrmann: Virchows Arch. f. path. Anat. **157**:297, 1899.

25. Curtis and Phocas: Contribution à l'étude des tumeurs mixtes de la parotide, Arch. prov. de méd. **1**:7, 1899.

26. Collet, André: Des tumeurs mixtes des glandes salivaires des levres, Thèse de Paris, 1895, no. 277.

27. Pitancé, J.-B.: Etude sur les tumeurs mixtes du voile du palais, Thèse de Paris, 1897, no. 610.

28. Cunéo and Veau: Sur l'origine branchiale des tumeurs mixtes cervicofaciales: branchiomes cervico-faciaux, Cong. internat. de méd., chir., Paris, 1900, vol. 10, p. 278.

29. Weishaupt, Elizabeth: Ein embryonaler Seitenganz des Ductus parotideus und seine Beziehungen zu einigen tumoren der parotis, Arch. f. klin. Chir. **100**:542, 1912.

30. Moral, Hans: Ueber die ersten Entwicklungsstadien der Glandula parotis, Anat. Hefte **47**:383, 1913.

often included in these tumors. This might explain the beginning of the process but certainly not the very complex differentiation that later occurs. As early as 1882, Clementz [15] expressed the opinion that cartilage in mixed tumors of the parotid might be formed from epithelial cells. In 1888, Carrière [31] studied ramifying cells in the cartilage of

Fig. 11 (path. no. 50579).—Comparative histology of benign mixed tumor in section and in tissue culture. The patient was a white woman, aged 35, with a small hard tumor beneath the right ear, present for ten years. On Nov. 11, 1931, a complete excision was performed.

A, section showing spindle and epithelial cells lying loose in the stroma.

B, tissue culture showing spindle and epithelial cells in the culture medium.

31. Carrière: Note sur le développement des cellules ramifiées du cartilage des céphalopodes et de leurs rapports avec certains éléments des chondrome, Compt. rend. Soc. de biol. **5**:577, 1888.

cephalopods and their relation to the chondrotomes. Ehrich,[32] in 1906, maintained that the cartilage resulted from a condensation and the chemical transformation of the epithelial cells which had undergone a mucoid degeneration. Alezais and Bricker [33] also upheld these views and attempted to correlate them with the work of Carrière, in that they believed that similar ramifying cells. of the type occurring in the cephalopods, occurred in tumors of the parotid.

A restudy of the microscopic material of the cases in the present series and tissue cultures from human tumors of the mixed type grown

Fig. 12.—Human embryo 4501 of 18 mm. Anlage of the parotid gland showing the continuity of the epithelial elements with the lining of the buccal cavity: *A,* anlage of the parotid gland; *B,* Meckel's cartilage, and *C,* buccal cavity.

in vitro showed that the actively proliferating tumor element is an elongated basal cell which transforms into a more cuboidal or more columnar type (fig. 11). This is borne out by the embryology of the salivary glands, which in their early stages are outpouchings of the buccal epithelium (fig. 12). It is apparently the outlying cords or strands of this glandular epithelium invading the connective tissue of

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32. Ehrich: Zur Kenntnis der Speicheldrüsentumoren, Beitr. z. klin. Chir. **51**:368, 1906.

33. Alezais and Bricker: Le cartilage a cellules ramifills des tumeurs parotidiennes, Compt. rend. Soc. de biol. **64**:380, 1908.

the capsule that is responsible for the beginning of the neoplastic process (fig. 14 *B*).

The tendency for the connective tissue components and their derivatives, myxoma and cartilage, to assume a prominent place in the microscopic composition of the tumor may be accounted for on embryologic grounds. Unlike the submaxillary glands, where such mixed tumors are relatively rare, the parotid from the earliest stages of its development lacks a specialized fibrous capsule (fig. 13). Instead, the epithelial cells diffusely invade the surrounding mesenchymal elements

Fig. 13.—Human embryo 5725 of 23 mm. Photomicrograph from the region of the jaws. The section shows the contrast between the early stages of development of the submaxillary gland *A* and the parotid gland *B*. Note the lack of encapsulation of the epithelial buds of the parotid and the definite formation of a capsule about the submaxillary gland.

in the region of Meckel's cartilage. From the first the parenchyma of the gland is thus closely associated with the precartilaginous structures of the mandible. This lack of definite encapsulation during development was emphasized by Löwenkron[34] and was noted by

34. Löwenkron, Hans: Ueber Entwicklung des Bindegewebes der grossen Mundspeicheldrüsen (bei menschlichen Embryonen), Ztschr. f. Anat. u. Entwcklngsgesch. **93**:370, 1930.
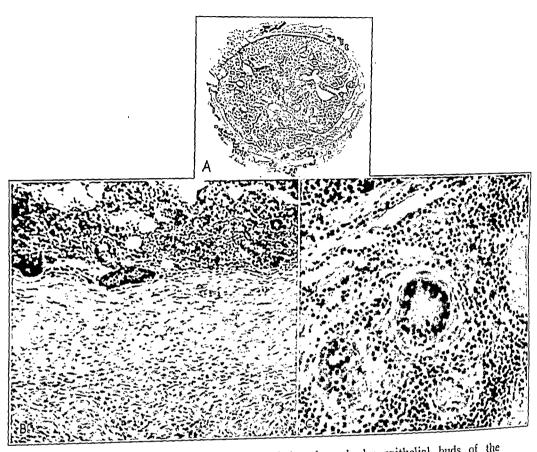
Fig. 14.—*A*, invasion of the normal lymph node by epithelial buds of the parotid gland in a human fetus of 21 cm. (After Neisse: Anat. Hefte **10**:287, 1898.)

B, photomicrograph of the margin of a normal lobule of the parotid gland in an adult showing the undeveloped buds of parotid epithelium at the capsule of the gland. Apparently these undeveloped buds of parotid tissue penetrate the surrounding capsule of connecting tissue, and the lymph nodes in the immediate region give rise to tumors of the parotid of the mixed type.

C, high power photomicrograph of a lymph node in the capsule shown in *B*. The illustration shows distinctly the invasion of the normal lymph node in an adult by the outlying buds of parotid epithelium, corroborating the findings of Neisse.

Delemare, Poirier and Cunéo.[35] Neisse [36] even observed invasion of the embryonic lymph nodes by normal epithelium of the parotid (fig. 14*A*). This tendency for the outlying acini of the gland to invade surrounding structures is seen in normal anatomic specimens that have been subjected to microscopic study (fig. 14*B* and *C*). During the process of

35. Delamare, Poirier and Cunéo: Anatomy of the Lymphatics, translated by C. H. Leaf, Chicago, W. T. Keener & Co., 1904, p. 250, fig. 94.
36. Neisse, R.: Ueber den Einschluss von Parotisläppchen in Lymphknoten, Anat. Hefte **10**:287, 1898.

tumor proliferation it is the outlying glandular elements (which normally retain the greatest growth potentialities) that are most active. Their invasion of the surrounding connective tissue apparently stimulates this precartilaginous substance to react and to proliferate. The result is a composite tumor of both epithelium and connective tissue.

PATHOLOGY OF CARCINOMAS OF THE PAROTID

The majority of the malignant tumors of the parotid are of the basal cell type (fig. 10). Although these tumors are usually adherent to the overlying structures, the skin is rarely ulcerated and there is no evidence to prove that these cancers arise from the basal cells of the epidermis. The carcinomas develop rapidly and are apparently circumscribed at first, but they soon become attached to adjacent structures, invade the gland, and finally involve the regional lymph nodes. Infiltration of the adjacent tissues is not infrequent in the malignant tumors, and occasionally the axillary and mediastinal lymph nodes are involved. Distant metastases are, however, extremely rare. Nasse observed local and general metastases that in 1 case extended to the bones. Although it was assumed on the evidence of gross pathologic examination that cartilage was present in 3 cases in the group of carcinomas, cartilage could not be found on microscopic examination. The fibrous constituents present are usually much overshadowed by the epithelial proliferation.

The microscopic structure may be that of an adenocarcinoma with cells of the columnar or basal form, but more often it assumes adenocystic basal cell features. This tendency for the undifferentiated tumors of the parotid to approach basal cell cancer in type is to be expected, since it is the basal cell layer of the primitive buccal epithelium from which the salivary glands are derived. The same tendencies for tumors arising in the appendages of buccal epithelium to give rise to adenocystic basal cell carcinoma is seen in adamantinomas derived from the epithelium of the gums and in aberrant mixed tumors in the mucous membrane about the cheeks and the palate. Carcinomas of this basal cell type frequently recur and extend locally, but rarely metastasize. It is usually the atypical carcinomas which give rise to widespread metastases, as illustrated in the case of L. S., a white man, aged 45 (fig. 9).

Anatomic Diagnosis.—The anatomic diagnosis was probable mixed tumor of the right parotid gland with malignant change. There was extension to the tissues of the neck and the axilla with metastases to the left axillary lymph glands, the right thoracic wall and the skin over the right side of the chest. Other findings were an x-ray burn on the right side of the chest, edema of the right arm, edema of the uvula and the larynx, a tracheotomy wound, aspiration pneumonia, edema of the scrotum and old syphilitic scars of the liver.

37. Footnote 37 has been deleted by the authors.

Clinical History.—The patient had mumps in early childhood, since which time a lump had persisted in the right parotid region. In December, 1925, the swelling began to increase in size, and irradiation was tried without success. An emergency tracheotomy had to be performed owing to acute dyspnea and edema of the face and of the right arm.

Physical Examination.—The temperature was 101.6 F.; the pulse rate, 120, and the respiratory rate, 30. There was an induration of the skin of the face and chest with small red nodules. The patient at first improved; then there was a recurrence of edema and dyspnea over a three day period. He was kept under the influence of morphine for two days, and died with a terminal rise of temperature to 108 F. His urine, Wassermann reaction and blood culture were negative. Biopsy showed a chronic inflammation and cells suggesting malignancy.

Autopsy.—A huge, firm mass was found in the region of the right parotid. The mass seemed to fade indefinitely into the indurated tissues of the neck. The skin of the neck was thickened, edematous and bluish red. The circumference of the neck was greatly increased and felt quite hard across the front and around the side beyond each ear. The tissues about the tracheotomy wound were thick and edematous with numerous firm white nodules in the skin over the entire left side of the chest down almost to the costal margin, which did not seem to extend beyond the midline. The tissue in the right axilla was very dense, and the right arm was swollen. An x-ray burn with large blisters on the left side in the axillary line was noted. When the soft tissue was stripped from the ribs, the muscles of the entire right side of the chest contained patches of firm white tissue similar to that of the skin. The mass in the parotid region was removed and found to be firm and rather hard with an indefinable outline. When the mass was removed, it was noted that the tumor tissue extended around the neck as far as could be explored, about 8 cm. behind the right ear. On the right side of the neck the muscles were infiltrated by the same dense white tissue that was found in the left axillary glands. The thyroid gland was surrounded by tumor tissue and on section showed firm, pale areas due to an infiltration of the new growth.

Microscopic Examination.—Sections from the skin, larynx, lymph nodes and parotid all showed the same type of cellular neoplasm. The predominant cell was round or cuboidal with a single or double large hyperchromatic nucleus (fig. 9). Small spindle cells and many lymphocytes accompanied the epithelial elements, which were arranged in partial acini or small islands. The microscopic diagnosis was cuboidal carcinoma of the parotid, or so-called atypical carcinoma.

DIFFERENTIAL DIAGNOSIS

In addition to the difficulty of distinguishing between benign and malignant tumors of the parotid gland, there is also the problem of differentiating these neoplasms from swellings in the parotid region caused by other conditions. In the differential diagnosis, the following conditions must be borne in mind: epidemic or infectious parotitis, benign or malignant lymphadenopathy, salivary calculus, Mikulicz' syndrome, actinomycosis, tumors of the jaw and antrum and peritonsillar and buccal abscess.

Epidemic Parotitis (Mumps) or Infectious Parotitis.—These conditions should cause little difficulty in diagnosis. Both are accompanied by an acute onset with fever, rather than by the gradual course char-

acteristic of parotid tumors. Mumps is distinguished by the bilateral involvement, the acute pain and the history of an epidemic in the neighborhood. Infectious parotitis is usually found in surgical cases in which the proper quantity of fluids has not been given.

Lymphadenopathy.—The occipital nodes and posterior auricular nodes may become enlarged as a result of leukemia, Hodgkin's disease, lymphosarcoma, syphilis, tuberculosis or acute infection, but in these cases there is an obvious enlargement of the other cervical glands at the same time.

Hodgkin's disease or lymphosarcoma may begin with marked swelling in only one group of nodes on one side of the neck. The swelling is, however, more rapid than in a parotid tumor and spreads more rapidly to lymph nodes elsewhere in the body. Palpation of the spleen and liver, a roentgenogram of the chest to determine whether or not there is a mediastinal tumor and a blood count to determine the possible presence of lymphoid leukemia are important procedures in making the differential diagnosis. The early response of malignant lymphoid tumors to high voltage roentgen therapy is diagnostic.

Salivary Calculus.—Salivary calculus occasionally may be present in the parotid duct, although it is more frequently found in the duct of the submaxillary gland. In the early stages it gives rise to sudden intermittent swelling of the affected gland when stimulus from food causes active secretion. If the process is of long standing, the gland may become permanently distended. Diagnosis may be determined by palpation, probing or roentgen examination.

Mikulicz' Syndrome.—This condition is characterized by chronic bilateral swelling of the parotid, and of the submaxillary, sublingual and usually the lacrimal glands. Sometimes there are associated splenomegaly and lymphadenopathy as well as changes in the blood picture. The syndrome is associated with lymphadenoma, lymphatic leukemia or chronic infection.

Actinomycosis.—This condition is uncommon and has occurred primarily in the parotid only fifteen times (in the literature). In other instances involvement of the parotid has been secondary. At first there is a hard, brawny induration of the skin and subcutaneous tissues, and later there are suppuration and frequently a granular exudation. Diagnosis is confirmed by the finding of the sulphur-like granules in which one can stain the mycelium; in the secondary form diagnosis is further facilitated by the presence of other areas of infection. Suppuration and ulceration found in actinomycosis are rare in parotid tumors.

Tumors of the Jaw and Antrum.—Tumors bulging the antrum or arising in the jawbone may be distinguished by palpation from neoplasms of the parotid because of their continuity with the bones of the face.

When this is not possible, an x-ray film depicting the osseous involvement will aid in making the distinction.

Peritonsillar and Buccal Abscess.—In peritonsillar abscess there is generally an antecedent history of systemic reaction such as is evidenced by fever, chills and aching. In addition, there are present pain and difficulty in deglutition, a fluctuant mass, which is generally soft, located in the peritonsillar area, and also leukocytosis. Pus may be obtained from such a mass by incision, and if early surgical procedure is not resorted to, spontaneous rupture is likely to occur.

In a case of buccal abscess there is generally a systemic reaction, and the patient often suffers from fever and chills complicated frequently by aching of the bones. On examination the area in question is found to be soft and fluctuant. Relief from symptoms rapidly follows incision and drainage.

TREATMENT

These tumors often resist even the most radical treatment and frequently recur, sometimes with a fatal result, in spite of the most careful therapeutic measures. There have been four methods in common use by which these tumors have been treated. Although the tables indicating this and the results are complete and speak for themselves, there are a few points that deserve discussion. The methods of treatment (fig. 15 and tables 1 and 2) used are:

1. Curettage
2. Enucleation
    (a) With resulting damage to the capsule [38]
    (b) Without damage to the capsule
3. Complete excision
    (a) Tumor and healthy tissue surrounding capsule
    (b) Use of cautery to excise
    (c) Phenolization or use of alcohol in tumor bed
4. Irradiation by radium or roentgen rays.

In 7 cases the tumor was removed in fragmented form by curettage with contamination of the tumor bed by tumor cells. Recurrence took place in all cases in which this method of treatment was used. This danger is apparently not obviated by doing a thorough curettage aided by Paquelin cautery, phenol and alcohol or zinc chloride (50 per cent), for even in 3 patients treated in this fashion there were recurrences.

Another unsatisfactory method and one by which many of these tumors have been removed because of fear of injury to the seventh nerve is that of enucleation by blunt dissection. This is a temptation

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38. The capsule referred to is macroscopic and not microscopic.

to even the most experienced of operators. It is, however, rarely achieved without some damage to the capsule, microscopic or macroscopic. This allows tumor cells to escape and become implanted, and because of this contamination of the tumor bed, a recurrence results. Of the 21 persons operated on by enucleation, only 12 were cured. Among those cured, enucleation in 1 was reinforced by the use of
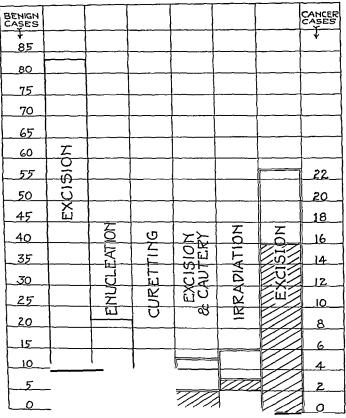

Fig. 15.—Chart showing the results of treatment in tumors of the parotid gland. To the left is shown results of treatment in the benign tumors and to the right the results of treatment in malignant tumors. The recurrences of the benign growths are indicated in black; the deaths in the cases of malignant tumors are indicated by the diagonal lines.

the cautery. In the others, it is practically certain that the enucleation was carried out without serious damage to the capsular structures.

Frequently the fibrous structures about these tumors appear to be bound down to the ramus of the jaw and to be intimately connected with the parotid gland, and often closely bound to the facial nerve. It is apparently when the mass is freed from these structures that implantation leading to recurrence takes place. One should attempt

Table 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid*

Path. No.	Age	Dura-tion, Mos.	Treatment	Date of Operation	Result
48157	39	72	Complete excision; capsule ruptured; ether placed in wound for recurrence; other operation 5 yrs. before; growth again 1 yr. ago	9/30/30	Oct., 1931: Well, but recurrence of tumor locally
47439	57	120	Complete excision with healthy margin	5/21/30	Oct., 1931: Well; no recurrence; well 1 yr. 5 mos.
46839	28	108	Excised piecemeal	2/ 8/30	Oct., 1931: Recurrence, general health good
46109	77	504	Enucleation; capsule damaged	1929	Oct. 25, 1931: Well; no recurrence
45609	70	12	Enucleation; alcohol placed in tumor bed	6/19/29	Oct., 1931: Well; no recurrence, 2 yrs. 3 mos.
43650	..	6	Excision	9/15/30	Aug., 1931: Facial paralysis; no recurrence following operation for recurrence 6/15/31
42968	54	72	Complete excision with parotid margin	1927	July 6, 1931: Well; no recurrence
42469	52	51	Complete excision with margin gland (then radiation) radium	12/ 2/27	
42317	55	216	Complete excision of tumor; no capsule damage	10/28/27	Oct., 1931: Well; no recurrence
42218	43	...	Complete excision; also radiation; radium	11/ 1/29	Aug., 1931: Well 1 yr. 9 mos.; no recurrence
42204	..	...	Complete excision	5/19/21	Aug., 1931: Well; no recurrence
41900	28	48	Complete excision; no capsule damage	6/25/29	Aug., 1931: Well; no recurrence
41862	..	42	Complete excision with healthy gland margin	4/19/29	July, 1931: Well; no recurrence
41699	25	60	Wide excision, phenolization..		
41496	65	24	Complete excision with surrounding margin for recurrence from operation 2 mos. earlier	4/ 4/29	Oct., 1931: Well; no recurrence
41330	22	43	Complete excision	2/ 4/29	Aug., 1931: Well; no recurrence
41273	20	24	Complete excision	4/27/27	
41218	57	...	Lumps appeared suddenly; decreased half under x-ray; completely excised	12/20/28	July 21, 1931: Well; no recurrence
40914	39	2	Complete excision for recurrence, 2 mos. following first operation	10/ 2/28	June, 1930: Well; no recurrence
38690	18	4	Enucleation three times.......	Sept., 1926-Feb., 1927	Aug., 1931: Recurrence; intensive radium treatment continued
38454	18	25	Complete excision with cautery; use of zinc chloride and alcohol	....	Sept. 4, 1926: Recurrence; reoperated on 11/1/26
38336	24	24	Complete excision with cautery of most of gland; ligation of duct	Nov., 1926	
38136	72	156	Excision	1926	Oct., 1931: Patient reported having died in 1930, 4 yrs. after operation; cause not stated
36730	38	48	Bilateral ligation of external carotids	11/ 6/30	Radiation caused no decrease of tumor; health poor
36438	19	14	Enucleation; capsule intact...	11/24/24	Jan., 1931: Well; no recurrence
36060	58	20	Complete excision for recurrence after 2 yrs. postoperatively	Nov., 1924	Oct., 1931: Well; no recurrence; basal cell features
36058	..	108	Complete excision for recurrence 9 yrs. after first operation	Nov., 1924	Aug., 1931: Well; no recurrence
35588	26	96	Complete excision with wide margin	6/11/24	Aug., 1931: Lower facial paralysis; well; no recurrence
35501	31	120	Complete excision with parotid margin	May, 1924	Partial facial paralysis; no word since
35308	62	24	Complete excision with parotid margin	3/12/24	Sept., 1931: Well; no recurrence

TABLE 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid*
—*Continued*

Path. No.	Age	Dura- tion, Mos.	Treatment	Date of Operation	Result
35113	48	2	Complete excision with gland margin for recurrence after 10 yrs.	3/13/24	Oct., 1931: Well; no recurrence
31593	52	120	Complete excision, third operation	4/11/29	No recurrence; died 22 mos. after operation, 6/2/31, of pneumonia
31384	58	...	Complete excision with gland margin	10/13/22	Oct., 1931: Well; no recurrence; numbness of tongue; paralysis of lips
28353	35	...	Complete excision third operation	....	July 15, 1921: Died of septicemia several days following operation
28324	23	...	Complete excision with gland margin	6/13/21	Well 4 yrs. 2 mos. later
28313	44	120	Complete excision	3/21/21	July, 1931: Well; no recurrence
28174	19	11	Enucleation; no capsule damage	May, 1921	Well, 1 mo. later
28078	28	36	Enucleation, capsule damaged	5/6/21	Jan., 1921: Well
27175	38	120	Complete excision with gland margin	Dec., 1920	March, 1921: Well; no recurrence
27014	60	96	Complete excision	Oct., 1920	Sept., 1929: Well; no recurrence; basal cell features
26856	61	24	Radiation	Sept., 1920	Oct., 1920: Tumor mass shrunken; abscess formation; death of cardiac decomposition Nov. 20, 1920
26732	29	30	Complete excision with gland margin	Oct., 1920	July, 1931: Well; no recurrence
26349	..	156	Excision for recurrence of tumor 15 yrs. after first operation	1920	Oct., 1931: Well; no recurrence
26213	50	168	Complete excision with gland margin	6/3/20	July, 1931: Well; no recurrence; complete facial paralysis since operation
25945	23	60	Excision piecemeal	4/16/20	Aug., 1921: Recurrence
23480	31	120	Complete excision with gland margin	July, 1918	Well, 1919; no recurrence
23146	40	36	Excision piecemeal with cautery; second operation	1/19/21	July 19, 1921: Facial paralysis; no recurrence; well
23032	27	60	Complete excision gland margin	4/10/18	April, 1919: Well; no recurrence
22695	45	16	Excision for recurrence 2 yrs. after first operation	Feb., 1918	Sept., 1931: Well; no recurrence
22579	66	9	Complete excision gland margin, third operation	Dec., 1917	Feb., 1926: Died of thrombo-angiitis obliterans and gangrene 8 yrs. 2 mos. after operation; no recurrence of tumor
22478	56	192	Excision; no capsule damage	11/13/17	Nov., 1919: Well; no recurrence
21990	60	240	Complete excision with cautery	8/14/17	Jan. 19, 1928: Death 10½ yrs. following operation
21110	58	2	Complete excision with cautery	3/8/17	May, 1918: Dead 14 mos. after operation, result of prostatic hypertrophy; no recurrence
20872	..	...	Complete excision	....	1931: Dead several years later, cause unknown
20163	..	156	Complete excision; no capsule damage	9/13/16	April, 1919: No recurrence; epilepsy, 1931; death about 15 yrs. following operation from unknown cause
19866	31	84	Complete excision	7/20/16	March 24, 1930: Dead of pelvic carcinoma 3 yrs. and 8 mos. following operation; parotid growth had not recurred

TABLE 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid*
—*Continued*

Path. No.	Age	Dura- tion, Mos.	Treatment	Date of Operation	Result
18295	45	96	Complete excision; third operation	Oct., 1915	Sept., 1931: Cysts in tumor area; facial paralyses have not increased in size since present 14 yrs. ago
17211	25	...	Excision; third operaticn....	3/22/15	Paralysis of face, no recurrence; committed suicide March, 1930, 15 yrs. following operation
17105	42	36	Complete excision; capsule damaged in wound	3/ 6/15	
16629	51	264	Enucleation; no capsule damage	12/12/14	Oct., 1931: Well; no recurrence
16543	44	144	Complete enucleation, no capsule damage	Oct., 1914	1919: Well; no recurrence
16467	21	84	Complete excision; no capsule damage	10/31/14	April, 1919: Well; no recurrence
16272	38	100	Complete excision; curettage	9/21/14	July, 1921: Well; no recurrence
16208	27	132	Complete excision; no capsule damage	9/ 5/14	April, 1919: Well; no recurrence
15233	..	84	Complete excision	Jan., 1914	May, 1919: Well; no recurrence
14695	52	360	Complete excision	9/27/13	May, 1919: Well; no recurrence
14689	77	8	Complete excision of tumor and gland margin with cautery for recurrence	7/13/25	1929: Well; no recurrence; conjunc. initiation secondary to facial paralysis
13575	45	7	Complete excision with cautery	12/14/12	1919: Well; no recurrence
12675	27	132	Complete excision with surrounding margin	4/20/12	1918: Well; no recurrence; Sept., 1931: well few years ago
12460	59	96	Excision with ligation of common carotid	2/20/12	Feb. 21, 1912: Dead from postoperative shock
12291	42	24	Complete excision for recurrence	12/16/11	Facial paralysis; Sept., 1931: well; no recurrence
11048	27	24	Enucleation for recurrence....	12/29/10	1912: Died during operation for recurrence
10031	36	60	Complete excision with margin for recurrence	10/16/09	May, 1919: Well; no recurrence
9784	54	2	Complete excision, cauterization and phenolization because of capsule rupture	5/27/09	Nov., 1920: Well; no recurrence
9518	40	24	Complete excision; capsule rupture; cauterization and phenolization	2/11/09	Oct., 1931: Well; no recurrence
9494	25	84	Complete excision; capsule rupture; cauterization and phenolization	2/ 1/09	Oct., 1931: Well; no recurrence
8989	57	36	Complete excision	6/ 8/08	1915: Killed in accident 7 yrs. after operation; no recurrence
8171	43	144	Complete excision	5/ 3/07	Oct., 1915: Well; no recurrence
8131	70	120	Enucleation; no capsule damage	4/19/07	1908: Well; dead before 1915, probably from apoplexy since patient had one stroke before operation; no record of recurrence
8127	72	216	Excision of parotid gland and chiseling away of ramus of the jaw	....	June 15, 1908: Death of chronic nephritis 1 yr. 4 mos. after operation; recurrence of tumor locally
7972	58	300	Complete excision	2/21/07	Feb. 21, 1907: Dead of bronchopneumonia
6706	69	240	Complete excision	9/13/05	June, 1907: Well; no recurrence; dead by 1923, cause unknown
6586	47	216	Excision piecemeal 2 yrs. after first operation for recurrence	1905	1915: Well 10 yrs., then recurrence; third operation June, 1920

TABLE 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid —Continued*

Path. No.	Age	Dura- tion, Mos.	Treatment	Date of Operation	Result
5490	45	156	Tracheotomy and enuclea- tion; no capsule damage	5/18/04	Sept., 1907: No recurrence; chronic nephritis
5417	17	12	Complete excision	4/15/04	1908: Well; died of extensive recurrent tumor locally 9 yrs. following opera- tion; no evidence of metastases
5167	65	36	Complete excision piecemeal by curettage	11/20/03	March, 1908: Well; death in 1909, 4 yrs and 4 mos. after operation; recur- rence; blindness 8 mos. preceding death
5044	43	36	Complete excision for recur- rence within 1 yr.	1/ 5/04	Oct., 1931: Well; no recur- rence; 50 per cent facial paralysis
5009	60	576	Complete excision with gland margin	8/24/03	July, 1907: Well; no recur- rence
4872	47	48	Complete excision	5/21/02	Oct., 1931: Well; no recur- rence
4861	24	100	Complete excision	6/ 1/03	1908: Well; no recurrence
4297	17	24	Complete excision, gland mar- gin	6/ 6/02	1916: Well; no recurrence
4231	77	540	Excision	4/29/02	1908: Dead due to other causes 6 yrs. after opera- tion; no recurrence
4227	35	108	Complete excision; resection, wiring of lower jaw and tracheotomy	4/20/02	1919: Dead from apoplexy 17 yrs. after operation; no recurrence of tumor
4040	58	240	Complete excision; facial nerve cut; also second oper- ation	11/27/01	1910: Recurrence; 1919: well; no recurrence
3973	20	240	Enucleation .... Complete excision	11/ 9/01 6/ 8/10	1910: Well; then recurrence 1919: Well; no recurrence
3282	27	108	Complete excision	9/13/00	March, 1908: Well; no recur- rence
3051	53	60	Complete excision; enuclea- tion	4/24/00	Oct., 1913: Well; no recur- rence
2911	21	84	Complete excision	1/19/00	1905: Well; no recurrence; temporary facial paraly- sis after operation
2756	53	72	Enucleation; division of pa- rotid duct	10/06/99	1905: Recurrence
2173	56	324	Enucleation; ligation of jugu- lar vein	4/15/98	1908: Died of other causes 10 yrs. after operation; no recurrence
1669	31	276	Complete excision	1/26/97	1905: Death of pneumonia 5 yrs. after operation; no recurrence
1578	26	120	Complete excision with gland margin	11/13/96	1919: Well; no recurrence; facial paralysis
S.N. 1491	55	120	Enucleation; no capsule dam- age	3/15/92	1915: Death from apoplexy 23 yrs. after operation; no recurrence of tumor
S.N. 1095	27	36	Complete excision	7/27/91	April, 1908: Well; no recur- rence
997	40	48	Complete excision; ligation of external carotid	7/19/95	Oct., 1931: Well; no recur- rence
803	20	24	Complete enucleation	3/ 9/95	June, 1897: Death 2 yrs. later following abdominal condition; no recurrence
S.N. 740	26	60	Complete excision with sur- rounding glands	12/ 2/90	April, 1919: Well; no recur- rence
605	23	96	Complete excision with gland margin	10/15/94	1908: Well; no recurrence; partial loss of sight of right eye and of hearing in right ear

TABLE 2.—*Results of Treatment in Carcinoma of the Parotid*

Path. No.	Age	Dura- tion, Mos.	Treatment	Date of Operation	Result	Time Well
43232	10	..	Incomplete excision; radium packs applied 3 times; no result; recurrence	Jan., 1930	Oct. 20, 1931: General condition good; no metastasis; no increase in size of recurrent growth; radium pack continued	1 yr. 9 mos.
42355	55	10	11/5/27: Second radical mastoidectomy; tumor material curetted out	11/ 5/27	Jan. 1, 1928: Died of pressure symptoms on brain; emanations for 8 hrs. had been of no value	2 mos.
41752	42	6	Complete excision with wide margin, cautery and knife	5/28/29	Sept., 1931: Well; no recurrence	2 yrs. 4 mos.
39344	30	3	Piece of tumor removed following excision of glands in neck and recurrence 2 mos. before; radium advised	April, 1916	Aug. 5, 1916: Death 4 mos. after operation much pain and distress	
36754	42	44	Complete dissection of scar, sternocleidomastoid muscle, internal jugular vein and all glands for recurrence	6/17/25	May, 1931: Poor health, great pain locally; recurrence last 3 yrs.; anemia, phlebitis left leg and gastro-intestinal upset	
36054	47	84	Excision of tumor 6 yrs. ago; recurrence 6 mos.; 5 series of x-ray treatments	1924-26	Aug., 1931: Death; carcinoma of large intestine; no recurrence of parotid tumor following disappearance on x-ray treatment	5 yrs.
35408	67	300	Complete excision of parotid area of skin; knife and cautery; 3 x-ray treatments before of no avail; recurrence after second operation for benign tumor; first 25 yrs. ago; second 10 yrs. ago; facial paralysis, 6 mos.	5/29/24	July 29, 1924: Dead	2 mos.
27755	50	36	Complete excision	Feb., 1921	Aug., 1921: Died 6 mos. following operation; huge recurrence	
27368	39	36	Complete excision with cautery; parotid gland removed in toto; division of 7th nerve	1/ 6/21	July, 1921: Well; no recurrence; facial paralysis	6 mos.
24680	42	144	Excision of mass posterior to parotid gland, into neck and about carotid artery	6/18/14	Aug. 17, 1919: Death; suffered a left hemiplegia immediately after operation; never rallied	
22521	59	8	Complete excision with parotid gland; cautery used	11/27/17	1921: Well; no recurrence	4 yrs.
21549	62	24	Complete excision of tumor and gland margin with cautery	5/18/17	April, 1919: Recurrence; quite ill; Oct., 1931: letter returned; patient dead; cause unknown	2 yrs.
1153	14	8	Complete excision of tumor and gland margin with cautery; also phenolization of tumor bed for recurrence	7/ 5/11	Patient died shortly thereafter; cause unknown	
9896	67	4	Complete excision	8/13/09	1912: Patient died; exact cause unknown	3 yrs.
9223	45	60	Complete excision; ligation of jugular vein for recurrence	9/15/08	1913: Recurrence; axillary mediast. metastasis in a few months; death about 5 yrs. following operation	
9216	33	4	Complete excision	9/11/08	Oct., 1931: Well; no recurrence	23 yrs.

TABLE 2.—*Results of Treatment in Carcinoma of the Parotid—Continued*

Path. No.	Age	Dura- tion, Mos.	Treatment	Date of Operation	Result	Time Well
9120	45	40	Irradiation; tracheotomy	Feb., 1926	Feb. 24, 1926: Death 1 mo. following treatment due to aspiration pneumonia and metastases	
8771	57	8	Complete excision with gland margin	2/20/08	Dead, date and cause unknown	
7969	61	144	Excision of tumor with part of ear and parotid	2/21/07	Sept. 20, 1908: patient dead	1 yr. 6 mos.
7547	62	12	Excision of tumor, intra- jugular vein, external ca- rotid artery, sternomastoid muscle and glands of neck	9/12/06	Feb., 1908: Death; local recurrence and internal metastases	1 yr. +
6798	..	..	Excision of tumor..........	1905	1913: Patient dead; cause unknown	8 yrs.
6468	44	10	Excision of tumor with por- tion of parotid, submaxil- lary gland and lymph glands of neck	6/15/05	1915: Well; though local recurrence since 1908	10 yrs.
5686	63	1	Excision of lymph glands of neck; because of involve- ment of glands, parotid tumor was not touched	1904	1905: Death 9 mos. after operation; x-ray caused parotid to dis- appear, but at death there was marked glan- dular enlargement and ascites	9 mos.
4736	58	2	Complete excision of tumor with glands of neck; ex- cision of glands of neck	3/24/03 5/ 2/03	Sept. 15, 1903: Death, exact cause unknown	5 mos.
4322	28	15	Excision of tumor with over- lying skin, also of gland along sternomastoid muscle	6/23/02	July, 1902: Partial facial paralysis; no note since	
3187	31	5	Excision of tumor of pa- rotid and phenolization, secondary to scaly con- dition of lobe of ear	6/29/01	June 9, 1902: Recur- rence of tumor; inoperable	1 yr.
2302	53	24	Complete excision of mass with parotid tissue and lymph glands; facial nerve divided	3/17/99	Feb., 1900: Death 11 mos. after opera- tion; obscure gen- eral asthenia	11 mos.
2132	74	1	Excision of tumor, skin and parotid tissue	3/ 4/98	Dead; partial facial paralysis after operation	
1427	48	14	Excision of recurrent tumor and glands of neck 1 mo. after first operation	7/21/96	1897: Patient dead 1 yr. after operation; cachexia and cere- bral symptoms	

to free the nerve, but care must be taken to see that it is not at the risk of recurrence. As Ochsner [39] pointed out, this is best accomplished by making a wide incision so that sufficient exposure is obtained, and then if any radicles appear to be adherent to any particular degree a proper dissection is more readily carried out.

A better method of treatment as attested by the results reported here is that of complete excision by sharp dissection. If the patient is seen early enough and the tumor has not yet become too large, this can be done effectively, a margin of healthy tissue about the capsule being included. In the smaller growths this gives assurance of a cure and

39. Ochsner, A. J.: Three Cases of Benign Lesions of Parotid Gland, Surg. Clin. Chicago 3:903 (Aug.) 1919.

offers the probability of no attending damage to the seventh nerve. Even if the mass has reached a rather large size, this method still offers hope of success, though there is a greater possibility of facial paralysis. In 83 persons treated in this manner, both with benign and with malignant tumors, there were 72 cures and 11 recurrences. Certainly this is as good a method as one could desire for the primary tumors. It is particularly efficacious when coupled with phenolization or the use of a 50 per cent solution of zinc chloride.

The most radical method, attended usually with even a higher percentage of cures than the foregoing one, is the use of the cautery to excise the tumor completely and widely. There are always much scarring and mutilation with this method, and practically invariably a facial paralysis. Of course, the percentage of cures is greater than by the other methods, and it may be the method of choice in the cases of recurrent tumors in which there is already a facial paralysis. If the tumor bed is thoroughly coagulated, there is no necessity for the use of chemical cauterization, but this may be used as an added precaution. When it has been used there have been good results.

Irradiation.—In mixed tumors irradiation in association with operation was attempted in 3 cases in this series. In 2 there was benefit, although it is doubtful how much credit may be ascribed to the operation and how much to the irradiation. At the Howard Kelly Hospital (Baltimore), irradiation of mixed tumors has not been highly successful in the past for the following possible reasons:

1. The tumor cells are too resistant.

2. The position of the gland in the parotid region does not lend itself well to cross-irradiation, so that very heavy doses cannot be administered without great damage to the skin.

3. Implants of radium may injure the facial nerve because of the close proximity of the implants to the nerve. For this reason, in a mixed tumor which can definitely be cured by complete excision, radium is less the instrument of choice than surgical intervention.

Large doses of external irradiation with a radium pack just within the limits of an erythema dose from several directions over a long period of time have been found to be of some benefit in isolated cases. In 1 case irradiation was carried out at weekly intervals for six months, and the tumor mass in that period of time was found to have been reduced from 5 cm. to 3 cm. in diameter. Implantation of radon has been attempted in some instances with good results over a period of from two to three years. This offers a palliative treatment of mixed tumors by irradiation, and in those persons who would prefer this to

the chance of operative complications as exemplified by facial paralysis or the much rarer salivary fistula, this may be carried out. Mixed tumors, however, may resume growth after reacting favorably for a time to external or interstitial irradiation.

In cases of carcinoma of the parotid, irradiation has been found to be of distinct advantage. In 1 case, clinically diagnosed as carcinoma, a huge infiltrating growth was nonencapsulated and attached to the surrounding structures. This neoplasm involved the whole gland, ear and mastoid region in a rapidly growing mass. Even the most radical opera-
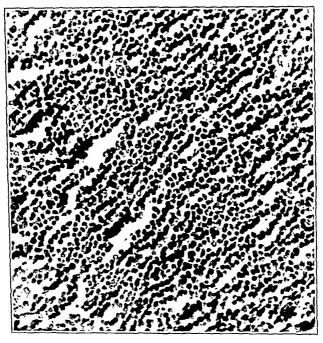
Fig. 16 (path. no. 36054).—Lymphosarcoma of parotid gland. A white man of 47 had a tumor of seven years' duration which recurred in spite of excision and high voltage roentgen therapy. Four series of high voltage roentgen treatments caused the ultimate disappearance of the parotid tumor and the enlarged cervical nodes. The patient died five years later of a so-called carcinoma of the large intestines. No autopsy was performed. The photomicrograph shows diffuse invasion of the parotid gland by typical lymphosarcoma.

tion offered little prospect of success. This tumor responded to the external application of radium. Rapid reduction in size was noted within two weeks, and soon the mass disappeared entirely. This patient has remained well three years.

In the series of cases of malignant growths in which radium therapy was attempted most of the lesions were advanced and many recurrent when the patients were first admitted to this hospital, and the treatment was combined with operation. One growth, which had recurred after an

incomplete operation, diminished slightly in size, and has been kept under control since, for a period of a year and a half, by repeated irradiation with radium packs. In 3 cases irradiation proved to be of no avail. However, in a case in which there was a recurrence six months after radical operation, roentgen therapy caused a disappearance of the growth, and the patient remained well for five years and died later supposedly of carcinoma of the intestine. Examination of the section showed the tumor to be lymphosarcoma (fig. 16).

The best results so far obtained by irradiation have been with the small round, cuboidal or spindle cell carcinoma of Chevassu—a malignant variant that has frequently been termed sarcoma. These cases yield favorably to irradiation, and good results may be seen within two weeks.

Secondary carcinomas of the parotid, particularly such tumors as those primary in the testicle and of embryonal type, melt rapidly under irradiation. Success may also be achieved in squamous cell carcinomas invading the parotid from the adjacent areas of skin.

CHOICE BETWEEN SURGICAL INTERVENTION AND IRRADIATION

The data on treatment in the present series of cases indicate the value of the judicious use of both irradiation and surgical intervention in tumors of the parotid gland. It is important in selecting the mode of treatment to distinguish between primary and recurrent tumors and between benign mixed tumors and carcinoma of the parotid. In small primary benign tumors complete excision by sharp dissection is the method of choice if this can be accomplished without danger to the facial nerve. In tumors that are infiltrating and malignant, a preliminary course of high voltage roentgen therapy should be given and a similar course of irradiation in all borderline tumors in which carcinoma is suspected. If shrinkage of the tumor occurs, substantiating the opinion of basal cell cancer, external irradiation should not be continued but should be followed by excision. In all recurrent tumors it would seem advisable also to administer a preliminary course of external irradiation for a short time (from four to six weeks). This should be followed by excision if the tumor is deemed operable, otherwise irradiation may be continued as a palliative measure, and in such cases there is no objection to fortifying the treatment by the implantation of radon. Where the tumor is under control with external irradiation, the danger of injury to the facial nerve must be considered before additional therapy is attempted in the form of surgical procedures or interstitial irradiation.

When excision of benign, recurrent or malignant tumors is attempted, with or without preliminary irradiation, the question arises

whether the tumor bed following excision should be cauterized or should receive irradiation.

Considering all the available data, the matter of combining roentgen therapy and surgical treatment can be summed up for the present as follows: Complete excision should be chosen for all benign operable tumors and irradiation as a palliative measure in all inoperable cases. In borderline cases, in recurrent tumors and in carcinoma of the parotid, external irradiation should be given as a therapeutic test or as preliminary treatment, followed by excision, reenforced with interstitial irradiation of the tumor bed in recurrent or malignant cases.

PRESERVATION OR SACRIFICE OF THE FACIAL NERVE

Besides the alternative between surgical intervention and irradiation, the question of preservation of the facial nerve must be kept constantly in mind in the treatment of parotid tumors. If the tumor is primary and benign and excision is determined on, should the operator in his dissection complete the removal of the tumor with the inclusion of a healthy margin when important nerve radicals pass into the tumor substance? Or should an attempt be made to spare the nerve by bisecting the tumor at this point, peeling it from the nerve and after the operation cauterizing the tumor bed with chemical applications such as a 50 per cent solution of zinc chloride or implanting radon seeds in the tumor bed? The latter procedures may be justified if the major radicals supplying the eye and the entire side of the face are involved, whereas a lower or less important filament may be sacrificed. Whether the prevention of deformity is worth the chance of recurrence must be decided by the surgeon in charge after a careful consideration of such factors as the age and sex of the patient, the social status and the microscopic structure of the tumor. In certain cases it may be advisable to postpone operation and attempt to control the tumor by external irradiation.

However, in all recurrent tumors and in all rapidly enlarging tumors with malignant features, the treatment should aim at eradicating the disease without regard to preservation of the nerve. The basis for this decision is the almost inevitable sacrifice of the nerve eventually with subsequent recurrences.

SUMMARY

The greater number of tumors of the parotid gland may readily be divided into benign mixed tumors and malignant basal cell neoplasms. The benign lesions are more frequent (83 per cent), occur in younger persons (from 21 to 45 years), have a slower rate of growth (average duration, eight years) and are usually circumscribed, firm, rubbery growths which on microscopic section have a large amount of connective

tissue and myxomatous stroma. The malignant lesions are less common (17 per cent), usually occur in persons over the age of 45 (from 45 to 65 years), have a more rapid rate of growth (average duration, four years) and are adherent, hard or soft growths which on microscopic examination have adenocystic basal cell features. The growths with basal cell features are more prone to recur after treatment. The benign mixed tumors are not truly mixed tumors but fibro-adenomas of the parotid gland in which the stroma is acted on by a salivary secretion from the adenomatous areas to produce the myxomatous or cartilaginous features.

Both surgical intervention and irradiation have their place in the treatment of these tumors. Small benign mixed tumors are best treated by complete excision with the knife, care being taken to preserve the facial nerve. The malignant tumors should be irradiated first and later excised if they become operable and freely movable. Otherwise palliative irradiation should be continued. Following the excision in operable cases, interstitial irradiation may be applied to the tumor bed.

COMPLETE REMOVAL OF TWO TUMORS OF THE THIRD VENTRICLE WITH RECOVERY

CLEMENT B. MASSON, M.D.

NEW YORK

The literature pertaining to tumors of the third ventricle is largely concerned with the various clinical syndromes, postmortem observations and histologic studies of the lesions and, only recently, with preoperative diagnosis and surgical removal of the new growths. It is not my purpose in this paper to give a résumé of the literature on the numerous clinical syndromes caused by tumors of the third ventricle, which have been so ably described by Weisenburg and by several others.[1]

As regards the early diagnosis of these lesions, one finds that the injection of air into the ventricles either by the direct or by the lumbar route, as first described by Dandy[2] in 1918 and 1919, respectively, is of the greatest help. Furthermore, the injection of dye into one lateral ventricle to determine the patency of the foramina of Monro has also contributed to the diagnosis of lesions obstructing one or both of these openings.

The successful treatment in the case herewith reported may not be applicable in every instance, so that no claim will be made that the technic employed is of general application or that all tumors of the third ventricle irrespective of their pathologic character are amenable to surgical attack.

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REPORT OF CASES

CASE 1.—*History.*—E. W., aged 20, from the neurologic service of Dr. Robert F. Sheehan, was admitted to Community Hospital on Sept. 23, 1932, and discharged on November 6. She was referred by Dr. C. S. Mirkin, who had treated her since 1930 for headache and tinnitus and nausea and vomiting in the morning. Her first symptom was a hammering sensation referred to the left vertex, which lasted for several weeks. There was diplopia for about three weeks during the first year of illness. In 1930, a lumbar puncture was performed which relieved her from all symptoms for one year. With the return of symptoms in November, 1931, frontal headaches were more pronounced than they had been previously and were noticeably worse a few days before the menstrual periods. The patient recalled having fainted three times and ascribed the attacks to her menstrual periods. On September 12, her physician performed a lumbar puncture which gave relief from symptoms for one week. Owing to the recurrence of symptoms, she was admitted to the hospital on September 23.

As a child she had suffered from measles, whooping cough, diphtheria and scarlet fever. Her family history did not indicate any nervous or mental disease.
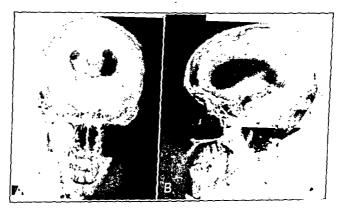
Fig. 1.—*A*, anteroposterior view showing the absence of a shadow of the third ventricle and curved deformities in the mesial inferior extent of both lateral ventricles. *B*, lateral view, showing markedly dilated lateral ventricles with no shadow representing the third ventricle.

Examination.—The patient was rather delicately built and was fairly well nourished, with no abnormal attitudes or deformities. She stood normally with eyes opened and closed, but in walking showed a tendency to fall to the left, especially on turning to the left. The nonequilibratory tests gave normal results. The deep reflexes were slightly increased in the left upper extremity, but in the lower extremities they were equally active; there were no abnormal reflexes. Her motor and sensory status was normal. The sense of smell was normal. The fundi showed some blurring of the disks save in a small temporal quadrant, where they were outlined; the veins were fuller than normal, but not tortuous. The visual acuity was 20/20, and the visual fields showed a slight enlargement of the blind-spots. The pupils were 5 mm. in diameter and reacted to light and in accommodation. The extra-ocular movements were normal save for a slight weakness of the right sixth nerve. The fifth and seventh nerves were normal. There was a mild middle ear deafness in the left ear; the right ear was normal, and the remaining cranial nerves showed no abnormalities.

Laboratory Examination.—The blood count showed a moderate secondary anemia. Urinalysis gave negative results. The spinal fluid was opalescent and contained 5 cells per cubic millimeter. The globulin test was negative; there was 25 mg. of protein per hundred cubic centimeters of fluid; the Wassermann reaction was negative, and the colloidal gold curve was 0-0. The Wassermann reaction of the blood was negative. Roentgenograms of the skull demonstrated no abnormalities other than a thinning of the dorsum sella. The manometric pressure of the spinal fluid was 580 mm. with the patient in the sitting posture. On October 6, roentgenograms taken after the removal of 78 cc. of fluid and the injection of 70 cc. of air by the lumbar route showed definitely dilated ventricles with poor visualization of the third ventricle. For this reason, ventriculography was carried out on October 11, with the patient under local anesthesia, according to the
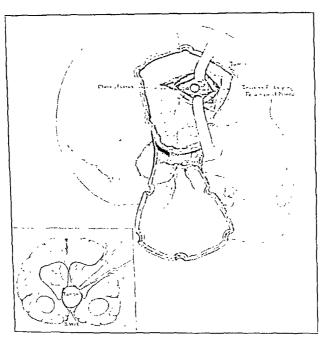
Fig. 2.—Lateral view showing the transcortical incision and exposure of the right foramen of Monro blocked by the tumor mass. Note that retraction was made upward and downward and not posteriorly, which would have endangered the motor cortex. The cross-section shows the manner in which the tumor capsule was delivered with a bayonet forceps through the enlarged foramen of Monro.

Frazier technic. The roentgenograms showed dilated lateral ventricles with the left larger than the right. The third ventricle was not shown, for there was a club-shaped defect in it, and the anteroposterior view showed a curved deformity in each lateral ventricle. These roentgenograms (fig. 1) warranted the diagnosis of a tumor of the third ventricle.

The results of the ventriculography were both interesting and significant. After trephination was done, the dura was felt to be under slightly increased pressure on both sides, and through stab wounds in the dura a brain needle was inserted into the right ventricle at a depth of 6 cm. and into the left at a depth of 4 cm.,

with the loss of a few cubic centimeters of fluid. Two cubic centimeters of indigo carmine dye was injected into the right ventricle and, after several minutes, a small amount of blue-tinged cerebrospinal fluid escaped from the needle in the left ventricle. Then the flow of blue-tinged fluid stopped, and the remaining fluid obtained from the left ventricle was clear and colorless. The fluid obtained from the right ventricle was of a deep blue. In all, 75 cc. was removed from the left ventricle and 27 cc. from the right. When a satisfactory replacement of air had taken place, the needles were withdrawn and the wounds closed. Since little dye entered the left ventricle by way of the foramina of Monro and the third ventricle, a ball valve closure of one or of both foramina was indicated. That the obstruction was not complete was also borne out by the patient's lack of papilledema and of signs of marked increased intracranial pressure.

Fig. 3.—Low power photomicrograph showing the contents of the cyst. Clefts filled with cholesterol crystals are seen in an amorphous eosinophilic material; the clefts in many instances are surrounded by giant cells.

The history and the few neurologic findings pointed to a midline lesion. However, the information gained during ventriculography and by examination of the plates led to a definite diagnosis of a tumor of the third ventricle. On October 15, with the patient under avertin anesthesia, a right osteoplastic flap was turned down without incident. The dura was tense and not pulsating. Through a stab wound in the dura a brain needle was entered into the right lateral ventricle, allowing the escape of air and thereby greatly reducing the intracranial pressure. The dura was opened in the anterior upper extent of the exposure horizontally from 3 to 4 cm. Then a vertical incision 1.5 cm. in length was made in the dura at right angles to the anterior extent of the horizontal incision, exposing a small triangular area of cortex.

The larger cortical vessels were controlled by clips, following which a horizontal transcortical incision 3.5 cm. in length was made by means of a high frequency

Fig. 4.—High power photomicrograph showing squamous epithelium lining the cyst.
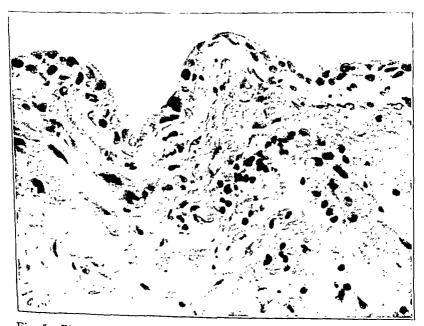
Fig. 5.—Photomicrograph showing a single layer of epithelium lining most of the wall of the cyst, with an infiltrated layer of heavy connective tissue beneath.

knife. The remainder of the transcortical incision was carried out with blunt disection opening into the anterior extent of the right lateral ventricle. By means of brain retractors, one retracting upward and one downward, a good view of the mesial wall of the right lateral ventricle was obtained, and a little farther posteriorly an enlarged right foramen of Monro was brought into view. The foramen was blocked by a round, bluish mass together with a piece of choroid plexus which came through the posterior extent of the opening (fig. 2). Several veins running along the mesial wall of the ventricle were clipped, and the foramen, which was 1 cm. in diameter, was enlarged anteriorly for a distance of 1 cm. by the use of electrocautery. The choroid plexus was adherent to the capsule of the tumor at the foramen of Monro, and before it was free from the tumor a clip was placed on the choroid to control bleeding. A stab wound was made into the presenting portion of the tumor, allowing about 2 drachms (7.5 cc.) of dirty, greenish-yellow material to exude, which was sucked away. On examination, the material was found to be largely crystals of cholesterol. After the greater part of the contents of the tumor was removed, that portion of the growth which seemed to be free was carefully brought through the enlarged foramen of Monro. A pedicle 4 mm. in diameter composed of whitish tissue containing several blood

Fig. 6.—A snapshot of the patient taken two weeks after operation. The arrows indicate the outline of the flap.

vessels formed its attachment to the floor or to the right lateral wall of the third ventricle. The pedicle was clipped, and the tumor cut free. Finally, the entire tumor capsule, save for the initial opening made for the purpose of emptying its contents, was delivered intact by means of a bayonet forceps through the enlarged foramen of Monro. There was no troublesome bleeding throughout the procedure, and after free irrigation of the ventricles they were filled with physiologic solution of sodium chloride. The edges of the transcortical incision were laid in apposition, and the dura was closed with interrupted black silk sutures. There was no apparent edema of the brain; the intracranial tension was decreased, and, therefore, no decompression was necessary. The bone flap was returned to its former position and was closed in the usual manner with interrupted black silk sutures. Removal of the tumor was accomplished in a one-stage operation lasting two and a half hours.

Microscopic Description (figs. 3, 4 and 5).—The specimen was a cyst attached to a section of the choroid plexus. The wall of the cyst was lined on its inner surface by epithelium which was from two to four layers in thickness in some areas, where it was seen to be squamous in type. For the most part this epithelial lining was single-layered and composed of flattened or cuboidal cells, some of

which were vacuolated. Many of the cells contained keratohyaline granules. External to the epithelial layer was a band of heavy, collagenous connective tissue, which was somewhat edematous, showed many small hemorrhages and was mildly infiltrated by lymphocytes, large monocytes and a few polymorphonuclear leukocytes. Within the cyst was a large mass of homogeneous and granular eosinophilic material within which were numerous clefts filled with cholesterol crystals, the clefts being surrounded in many cases by foreign body giant cells. There was an ingrowth of capillaries and connective tissue into this central mass from the cyst at one point. In the contents of the cyst were also a considerable number of large mononuclear phagocytes containing hemosiderin. The diagnosis was epidermoid cyst.

Course.—Postoperatively, the patient was disoriented as to time but correctly oriented as to place and as to person. She talked somewhat irrationally for several days but within two weeks was approximately oriented and read the newspaper intelligently. The deep reflexes were increased on the left. There were slight left lower facial weakness and a decrease in strength of the grip of the left hand. However, the motor weakness disappeared at the end of the first week. She was able to sit up and walk about her room on the tenth day. On October 31, an encephalogram was made, 108 cc. of fluid being removed and an equal amount of air injected. With the patient in the sitting posture, the manometric pressure was 280 mm., which was 300 mm. less than the manometric pressure taken in the same manner before the tumor was removed. Air escaped over the cortex, and it was impossible to demonstrate any of the ventricles properly. The patient (fig. 6) was discharged on November 6 relieved of her former complaints. Her family physician reported that on November 21 he found that she had gained weight and strength to such an extent that she was able to play the piano for him and showed no mental disturbances. On Jan. 11, 1933, she returned to the follow-up clinic stating that she felt entirely well and had not felt so well for the past three years. There were no signs of organic neurologic involvement; vision was 20/20, and the fields were complete.

Dr. Cornelius G. Dyke assisted in the roentgenologic studies and Dr. Abner Wolf in the histologic work on the tumor that was removed.

This case demonstrates (1) the value of laboratory procedures in the early diagnosis of a tumor of the third ventricle; (2) that a tumor of the third ventricle may be removed in a one-stage operation and without the sacrifice of a large area of cortex, and (3) that the good postoperative result was due to the removal of the lesion before serious and irreparable injury to the brain had occurred directly by pressure or indirectly through the production of a marked hydrocephalus.

CASE 2.—C. C., aged 33, was admitted to the Neurological Institute on April 28, 1933, and was discharged on June 4. The present illness began in 1928, when the patient suffered from severe frontal headaches which lasted a week. She remained well until March 5, 1933, when she again suffered from headaches and had a series of convulsions, the details of which were not available. After the convulsions vision began to fail and vomiting occurred irregularly for two weeks. Early in April, she was admitted to another hospital and was seen by me. Papilledema with hemorrhages was present, but no other definite signs were elicited, and a ventriculogram was decided on to localize the lesion. Since by this time the patient

felt better she left the hospital against advice and attended two other clinics before being admitted to the Neurological Institute. She was cheerful, able to walk about and free from all symptoms save impaired vision.

The patient's past history was unimportant. She had five healthy children. Her father died of pellagra and her mother died from an unknown cause. One brother and three sisters are living and well.

Neurologic examination revealed a well developed, well nourished woman who cooperated well and showed no abnormal attitudes or deformities save a midline abdominal scar of a previous appendectomy. Her gait and station were normal. There were no changes in coordination; skilled acts were normally performed, and there were no abnormal involuntary movements. The deep reflexes were slightly more active on the left than on the right side. The left lower abdominal reflex was the only one obtained. Plantar flexion was present, and there were no abnormal reflexes present. Motor power was preserved; the muscle status was normal; there were no signs of meningeal irritation, and the sensory status was
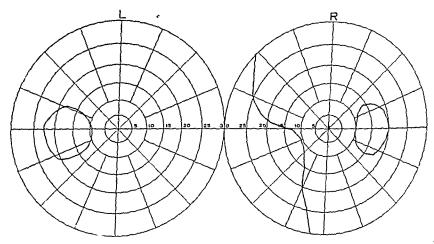
Fig. 7.—Visual fields on April 28, 1933, before operation: tangent screen, 1 meter; vision in the left eye, 20/50; in the right eye, 20/40; test object, 1 mm., white. The test was made in daylight, and the patient gave good cooperation.

normal. The cranial nerves were normal save for the presence of a papilledema of from 2 to 3 diopters. Vision in the right eye was 20/40, and in the left eye, 20/50. The visual fields (figs. 7 and 8) showed a lower nasal quadrant defect in the right field and bilateral enlarged blind spots.

The patient's mental status and laboratory status were normal. Roentgenograms of the skull showed the vault to be of average thickness and not unusual in size or shape. The floor and dorsum sellae were distinctly atrophic, and the posterior clinoids were slightly atrophic. Both mastoids were of average size, and the cells appeared clear. The pineal body was not visible. There was a small plaque of calcification in the meninges in the left posterior frontal region. The vascular channels and sutures did not appear abnormal. The sphenoid and petrous ridges appeared equal. The impression was that of an unlocalizable tumor of the brain, as indicated by the atrophic sella.

Clinically, the patient was considered to have either a tumor of the third ventricle or a bifrontal one, and therefore an injection of air was considered necessary. A ventriculogram was carried out on May 10, by means of bilateral punctures of

the posterior horns, at which time 55 cc. of fluid was removed from the right ventricle and about 110 cc. from the left ventricle. Air injected into one ventricle flowed freely from the needle in the other ventricle. The roentgenograms showed that both lateral ventricles were considerably dilated. They occupied their normal position. There was a concave margin to the medial aspect of the right lateral ventricle, demonstrating how a change in the pressure in one ventricle may alter the appearance of the medial aspect of the other ventricle. Only a small amount of air was noted in the third ventricle, and this was in the suprapineal recess. Both temporal horns appeared to be normal. The aqueduct and fourth ventricle were normal, and there was some air in the sulci, particularly over the left hemisphere. The impression was that there was a tumor of the third ventricle.

Since the diagnosis was definite from the laboratory standpoint and since this did not contradict the clinical findings, the patient was operated on for a tumor of the third ventricle. Only a partial first stage, right osteoplastic flap was accomplished under ether anesthesia. A general anesthetic was decided on because
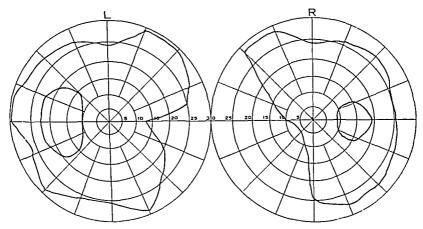
Fig. 8.—Visual fields on May 29, 1933, after operation: tangent screen, 2 meters; vision in the left eye, 15/40; in the right eye, ability to count fingers at 20 feet; test object, 2 mm., white.

of the patient's poor cooperation and fatigue following ventriculography. A small anteriorly placed right flap was outlined and several trephine openings were made, when the patient's respirations became 60 per minute. The wound was therefore closed, and the patient returned to the ward to await a more favorable time to complete the operation.

On May 17, the patient was operated on again under local anesthesia. The bone flap was reflected without incident, and the dura found under moderately increased pressure. A horizontal incision 4 cm. in length was made in the dura over the middle of the right frontal lobe, 3 to 4 cm. from the sagittal sinus. The posterior extent of the incision was well anterior to the motor area. At right angles to the anterior end of the dural incision two vertical incisions each 1 cm. in length were made in the dura upward and downward. This exposed a triangular area of cortex with its base directed anteriorly. Two large cortical vessels were clipped, and the cortex was incised with a Bovie knife to a depth of 1 cm. for about the length of the horizontal dural incision. By blunt dissection, the remaining subcortical tissue was incised, and at a depth of 4 cm. the right lateral ventricle

was entered. To gain an exposure brain retractors were inserted, the incised brain tissue being held upward and downward so that no pressure was made at any time against the motor area. After the right lateral ventricle was emptied, the right foramen of Monro was readily seen, and just within was a round plum-colored mass. Dilated veins coursed along the mesial wall of the ventricle, and these, together with the choroid plexus extending forward, entered the foramen. With the Bovie knife, the foramen was enlarged anteriorly by an incision 0.5 cm. in depth. Several large veins were in danger of being injured, and those adjacent to the tumor were clipped. The choroid was found intimately attached to the tumor, and was clipped in two places as it entered the foramen, allowing the tumor to be cut free between the clips. With a bayonet forceps, the tumor was found to be more or less cystic, free anteriorly and laterally and adherent posteriorly.

A stab wound was made in the presenting rounded surface of the tumor mass which was found to be about the size and color of a white grape. The contents of the tumor were too gelatinous to flow out, but were carefully scooped out with a curet. Then the entire capsule with some of the remaining substance of the
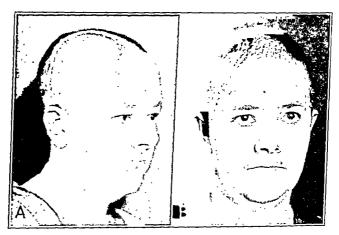
Fig. 9.—*A*, the flap on the fourteenth postoperative day. *B*, front view of the flap on the day of discharge.

tumor was gently delivered through the foramen by means of a bayonet forceps. A few fine adhesions that held the tumor posteriorly gave way with no bleeding as a result.

In removing cotton wall-offs, a vein anterior to the foramen of Monro was injured, which gave troublesome bleeding necessitating numerous cotton pledgets, irrigation and finally a small piece of muscle to bring it under control. When all bleeding was under control and wall-offs removed, the ventricle was filled with physiologic solution of sodium chloride and the edges of the cortical incision allowed to come together. The dural incisions were closed with interrupted black silk sutures and the flap returned to its former position and closed with interrupted black silk sutures. Throughout the operation, which lasted three hours and twenty minutes, the patient's condition remained good. No change occurred in the motor power of the left side of her face or her left arm or leg during the operation or at any time postoperatively.

Microscopic examination showed about the margins of a large mass of pink homogeneous material a narrow band of tissue thrown up in many papillary folds. The papillae were covered by one or more layers of epithelium lying on a base

of vascular fibrous tissue. For the most part this epithelium was cuboidal and lay on a band of connective tissue fibers. In some zones the epithelium was columnar and ciliated and lay on a base of glial fibers.

The diagnosis was papilloma of mixed ependymal and choroidal origin.

The patient made an uneventful recovery (fig. 9). On May 23, she demonstrated that she could read newspaper print, which she could not do before the operation, and on May 27, she was allowed to sit by her bedside. Contrary to routine instructions in the ward, however, she had been up and walking about on the first, fifth and seventh postoperative days because she wanted to go home or to wait on some nearby patient. On May 31, while eating her breakfast in bed, she became dizzy, fell forward and was unconscious. She said that the bed seemed to be tilting backward and that she felt ill for about fifteen minutes. The bone flap appeared to be elevated. A lumbar puncture was performed. The initial manometric pressure was 280 mm., and after 20 cc. of clear colorless fluid was withdrawn, the pressure was 140 mm. On the following day, the manometric pressure was 60 mm. No further attacks occurred, and the patient was discharged on June 4. She felt very well and showed no mental or neurologic signs. The papilledema had receded so that the outlines of the disks were visible. Follow-up examinations (the most recent one, September, 1933) have shown that the patient remains well.

In these two cases, the tumors of the third ventricle were successfully removed by the same technic. Both were in the anterior part of the third ventricle. In retrospect, it appears to me that a much smaller bone flap would answer every purpose, for only a limited extent of the dural exposure was used in each instance. It does not matter, therefore, how wide a dural exposure is provided since the tumor and its attachment to the third ventricle are just as deeply situated and cannot be drawn to the surface until freed. It is imperative that one work carefully at a distance. Irrespective of the size of the craniotomy, one finds oneself working at a distance from the root, and one has to depend on careful technic to be successful. If the lesion is totally extirpated, a decompression is not required, since the cause of the increased intracranial pressure has been removed.

53 East Sixty-Sixth Street.

SUPRAPERIOSTEAL AND SUBCOSTAL PNEUMONOLYSIS WITH FILLING OF PECTORAL MUSCLES

JOHN ALEXANDER, M.D.
ANN ARBOR, MICH.

Supraperiosteal and subcostal pneumonolysis with a filling of the pectoral muscles may be defined as the freeing of the anterolateral portions of the upper ribs from their periosteum and intercostal muscles and the tucking of the pedicled pectoral muscles between the bared ribs externally and the periosteum, intercostal muscles, pleurae and lung internally.

This procedure is chiefly indicated for cavernous tuberculous or nontuberculous lesions that lie between the clavicle and the level of the third rib anteriorly. The relaxation and rest of the lung that are produced, with or without the aid of hemidiaphragmatic paralysis, tend to check the advance of the pulmonary lesions and to close pulmonary cavities, or to favor the development of fibrous tissue that will do so.

Classic extrapleural pneumonolysis consists in resection of a portion of a rib anteriorly or posteriorly, splitting of the deep periosteum and manual separation of the parietal pleura from the ribs and intercostal muscles. The extrapleural space thus created is then filled with paraffin of 51 C. melting point, masses of fat, gauze, air, rubber dam, an inflatable rubber bag or the pectoral muscles. Each of these "fillings" has its present-day advocates. The direct separation of the parietal pleura from the thoracic wall is a genuinely useful operation. In my experience, paraffin has proved to be the most useful substance for filling, but it has the obvious disadvantages common to any foreign body that is expected to remain in the tissues. Furthermore, stripping of the parietal pleura from the thoracic wall may result in dangerous tearing of the pleura or pleurae and lung, and because of extrapleural inflammatory adhesions it is not always possible to effect separation to the desired extent.

Shivers,[1] Archibald,[2] Goffaerts and de Winther[3] and Sebrechts[4] have been the chief advocates of the use of pectoral muscles to fill an

1. Shivers, M. O.: Surgical Treatment of Pulmonary Tuberculosis, Colorado Med. **16:**27 (Feb.) 1919.

2. Archibald, E. W.: Extrapleural Thoracoplasty and a Modification of the Operation of Apicolysis, Utilizing Muscle Flaps for Compression of Lung, Am. Rev. Tuberc. **4:**828 (Jan.) 1921.

3. Goffaerts and de Winther: L'apicolyse dans le traitement de la tuberculose pulmonaire, Presse méd. **35:**1301 (Oct. 26) 1927.

4. Sebrechts, in discussion on Bérard and Lardinnois: Traitement chirurgical de la tuberculose pulmonaire, Presse méd. **37:**1334 (Oct. 12) 1929.

extrapleural space such as has just been described. Archibald resects portions of the second, third and fourth ribs anteriorly. Goffaerts and de Winther resect the third rib from the sternum to the "axillary line," and after performing pneumonolysis directly over the parietal pleura they make an incision in the first intercostal space, pull the pectoral muscles through this and arrange and fix them; in a large number of their cases a complicating extrapleural effusion caused them to open the wound widely and to pack it. It must be difficult or impossible to maintain the muscles snugly in position at the limits of the extrapleural space, especially in the dome of the thoracic cavity.

The disadvantages and dangers of creating for the pectoral muscles a space that lies directly on the parietal pleura prompted me more than six years ago to devise the operation that is the subject of this article.

The indications for it are, broadly, those that govern the use of paraffin in extrapleural pneumonolysis. Such simple measures as a fair trial of the regimen at the sanatorium, induced pneumothorax and perhaps interruption of the phrenic nerve together with scaleniectomy should be undertaken before pneumonolysis is resorted to. The pulmonary cavity to be closed should be in the upper part of the lung and be small or medium-sized, because extrapleural pneumonolysis rarely closes a large cavity, but tends to displace it downward. The majority of the infiltrative lesions should likewise be limited to the upper part of the lung. These conditions being fulfilled, the greatest value of pneumonolysis is for those cases of tuberculosis in which active disease in the opposite lung contraindicates even partial thoracoplasty. An occasional indication exists for patients with a small chronic cavity in whom there is no contraindication to thoracoplasty but in whom pneumonolysis appears to be a safer operation than thoracoplasty. The safety and effectiveness of the modern many-stage extensive thoracoplasty make a partial or complete thoracoplasty almost always the preferable operation, provided that there is no direct contraindication to it.

The use of supraperiosteal pectoral pneumonolysis is unfortunately limited by certain conditions that do not limit the classic operation of pneumonolysis. It is not applicable to cavities that extend above the level of the clavicle or to cavities that lie posteriorly rather than anterolaterally. The volume of the pectoral muscles must be sufficient to relax the diseased lung to the requisite extent, even though some atrophy may occur from pressure and disuse in spite of maintenance of the muscles' principal nervous and blood vascular supply. The introduction at one operation of a sufficient volume of muscle to close the pulmonary cavity is dangerous to a cardiocirculatory system the func-

tional reserve of which is insufficient to endure the sudden increase of intrathoracic pressure. This disadvantage is common to thoracoplasty performed in too few stages and to all fillings that are used with extrapleural pneumonolysis, with the exception of gauze, crumpled rubber dam and rubber bags, the volume of which may be gradually increased, but at the cost of an open wound. In five of my seven patients on whom pectoral pneumonolysis was performed there was surprisingly little immediate or delayed reaction to the operation. In one patient, who was a poor risk from the cardiocirculatory standpoint, the pulse was irregular for one day after operation and then became normal. One patient died, presumably as the result of pressure on her mediastinum. It would appear to be wise to use less than the entire pectoralis major as a filling if it is abnormally voluminous and if there is doubt about the patient's cardiocirculatory reserve.

It is obvious from the number of restrictions that are placed on the indications for supraperiosteal pectoral pneumonolysis that relatively few patients present suitable conditions for it. Since I first used it on May 12, 1927, I have performed the operation on only seven patients among eleven or twelve hundred who have been operated on for tuberculous or nontuberculous suppurative pulmonary disease. The operation is, however, sufficiently valuable for the occasional patient to justify its being reported.

Its chief advantages are: 1. It is simpler than other methods of using the pectoral muscles as a filling after pneumonolysis. 2. The lung may be freed from the ribs as widely as desired, and its collapse is therefore not dependent on the absence of tough extrapleural adhesions, which not rarely prevent an adequate pulmonary collapse in extrapleural pneumonolysis. 3. There is virtually no danger of wounding the pleura and lung, as the pleura is not even exposed. The operation may, therefore, be safely used in the presence of partial pneumothorax. 4. As no rib is resected, the filling is efficiently retained, and the expectorating mechanism, which is important in the prevention of stasis pneumonia, is but little interfered with. 5. The periosteum of the bared ribs is pushed deep into the thorax and presumably forms new ribs within approximately six weeks, which tend to maintain the lung in the collapsed position even though the muscles atrophy.

Lilienthal[5] has used temporary supraperiosteal packing after resection of ribs. Felix Miller[6] and Haight, Harvey and Oughterson[7] have

5. Lilienthal, Howard: Tuberculosis of the Lungs: Apicolysis by Two Different Methods, S. Clin. North America 8:235 (April) 1928.

6. Miller, Felix: Presentation Before the Texas Surgical Society, Feb. 3, 1930, Collected Proceedings of the Texas Surgical Society, to be published.

7. Haight, Cameron; Harvey, S. C., and Oughterson, A. W.: Surgical Treatment of Peripheral Lung Abscess: Extrapleural Compression with a Rubber Bag. Yale J. Biol. & Med. 3:235 (Jan.) 1931.

used the principle of my technic but substituted an inflatable rubber bag for the pectoral muscles as a filling.

OPERATIVE TECHNIC

The operation is performed under gas anesthesia with the patient in about a 15 degree Trendelenburg position. This aids the pulmonary secretions to gravitate toward the mouth and lessens the chance of their entering uninfected portions of the lungs. The incision, indicated in figure 1, is made to the pectoral fascia, and the skin and subcutaneous fat are then lifted from the entire surface of the pec-
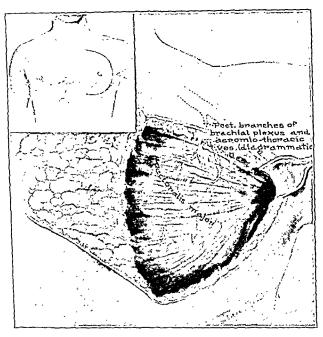
Fig. 1.—Cutaneous incision. The position of chief nerves and vessels (acromio-thoracic axis) of the pectoral muscles is indicated.

toralis major muscle. The costal and sternal, but not the clavicular, portions of the pectoralis major are then separated from their origins, and the humeral tendon is divided near the bone. The pectoralis minor is then separated from its ribs of origin; its insertion into the coracoid need not be divided. Care is taken that the principal neurovascular supply of the muscles (the external and internal anterior thoracic nerves and the pectoral branches of the acromiothoracic axis) is not injured because on its integrity as a pedicle depend the viability of the large muscular mass and its protection against rapid atrophy.

The pedicle pectoral muscles are turned upward (fig. 2) and protected with a warm moist cloth. Next, the periosteum is stripped from the anterolateral portion of those ribs that overlie the cavity and its neighboring lung. In three cases this included the second and third ribs and the inferior edge and posterior surface of
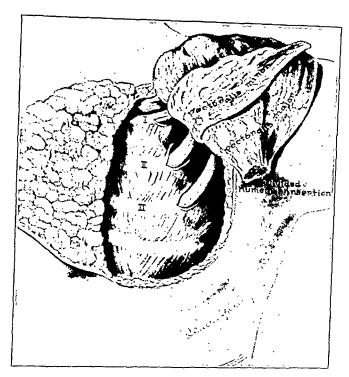
Fig. 2.—All of the pectoralis major, except its clavicular fibers, has been detached from the thoracic wall and humerus. The pectoralis minor has been detached from the ribs but not from the coracoid process. The chief neurovascular pedicle of both muscles is intact. Parts of the upper three ribs have been freed from their periosteum. The periosteum, the intercostal muscles and the underlying lung have been retracted from the bare ribs.
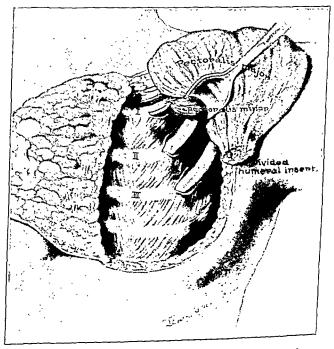

Fig. 3.—The pectoralis minor has been tucked into the first intercostal space and tacked in place under the first rib.

the first rib (fig. 2). In one case it included also the fourth rib; in another case only the second, third and fourth ribs were freed, and in two cases only the first and second ribs. Separation of the periosteum of the first rib is facilitated by having the arm well abducted; care must be taken not to injure the first portion of the axillary vein. The portions of the ribs that have been freed from their periosteum undergo gradual atrophy (fig. 5), but in none of my cases have they necrosed and sequestrated.

One of the chief limitations of this operation is that it is indicated only for cavities that do not extend above the clavicle, because separation of the lung and pleurae together with a protecting layer of soft tissues is not possible above the superior edge of the first rib. If an extrapleural space were to be created between
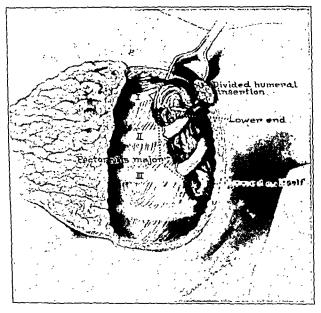
Fig. 4.—The pectoralis major was pulled through the first intercostal space, downward beneath the second and third ribs and out through the third intercostal space. Its deep surface was then stitched to the periosteum of the fourth rib and the redundant muscle pulled upward beneath the third and second ribs and stitched to itself in the first intercostal space. A drain for serum was placed dependently in the axilla.

the first rib and the dome of the thorax, the periosteum of the first rib would need to be divided and separation of the lung and pleura from the thoracic wall continued in the endothoracic fascial tissue, as in the classic type of extrapleural pneumonolysis. This combination of the two types of operation is probably feasible, but I have not yet used it.

After the anterolateral portions of the first, second and third ribs have been freed from their periosteum, the periosteum and intercostal muscles between the fourth rib and the superior edge of the first rib fall far away from the bare ribs. Obviously, the volume of the underlying lung is reduced, and the walls of the contained cavity, if not too rigid, approach one another.

The next step in the operation is to tuck the pectoralis minor into the first intercostal space and between the first rib and its separated periosteum, and to tack it in place with one or two sutures between it and the unseparated periosteum laterally on the lower edge of the first rib (fig. 3).

The lower edge of the pectoralis major is seized by two hemostats which have been passed upward, deep to the bared ribs, and gently drawn backward by means of a wiggling motion of the hemostats through the first intercostal space, then downward behind the bared ribs and in front of the insunken periosteum and intercostal muscles, and finally forward through the third intercostal space. The deep surface of the muscle is tacked with a few catgut sutures to the periosteum of the upper edge of the fourth rib, and the edge of the muscle is again seized by hemostats, this time introduced from above, and is drawn upward just behind the third and second ribs to the first intercostal space, where it is tacked to itself (fig. 4).
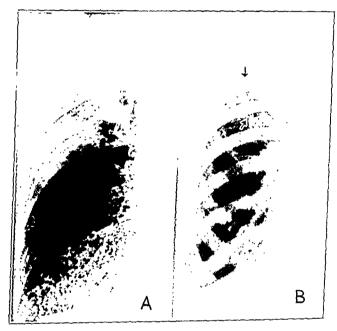
Fig. 5.—*A*, a nineteen month old nontuberculous abscess, filled with iodized oil, in a 53 year old man; 120 cc. of foul sputum was expectorated. The onset was gradual, probably secondary to a diseased mouth. Induced pneumothorax was unsatisfactory. *B*, the area three years after supraperiosteal pectoral pneumonolysis. There was no sputum or symptoms. The upper arrow indicates the spur of the regenerated periosteum. The lower arrow points to marked atrophy of the second rib; the third rib is atrophied to a less extent.

Beneath the anterolateral portions of the upper three ribs there are now the pectoralis minor and a double thickness of the pectoralis major muscles.

Wiggling the pectoralis major through the first intercostal space caused a fracture of the atrophic second rib in the case of a 56 year old man; this made no apparent difference in the postoperative course.

A stab incision is made in the posterior cutaneous flap for serum drainage of thirty-six hours' duration, and the cutaneous incision is closed. A snug pressure dressing is applied. In none of the seven patients has there been any infection of the wound.

The postoperative care is the same as after a radical resection of the breast, and the ultimate function of the arm is the same (fig. 7).

The sudden reduction in volume of the diseased lung causes its secretions to flood the bronchi, and it is therefore important that the patient expectorate as completely as possible as soon as he awakens on the operating table from the gas anesthesia, and that he continue to expectorate freely during the postoperative period. Immediately before operation he should have coughed up all loose sputum.

Seven patients have been operated on by this technic. One, a man of 53 with arteriosclerosis, had a foul nontuberculous abscess (fig. 5) of nineteen months' duration, twelve months of which he spent in a sanatorium. After operation improvement was rapid at first, then gradual; three years after operation the patient had no sputum and was apparently cured. On three of the six tuberculous patients the operation was intentionally done preliminary to thoracoplasty in order to displace
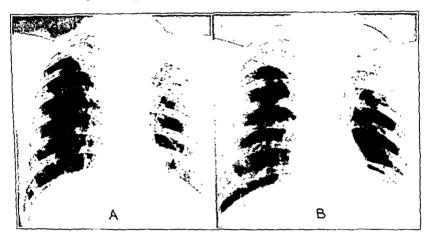
Fig. 6.—*A*, bilateral tuberculosis of seven years' duration in a 24 year old man. There was marked loss of weight, and 150 cc. of sputum positive for tubercle bacilli was expectorated. On the left side there is a chain of four cavities between the first and fourth ribs anterolaterally. The patient had failed to benefit markedly from several residences in sanatoriums. Pneumothorax could not be induced because of adhesions. Thoracoplasty was contraindicated because of active tuberculosis in the right lung. *B*, seven months after supraperiosteal pectoral pneumonolysis no cavity was visible. Within six months after the operation the patient had gained 35 pounds and during the last four months his sputum had been repeatedly negative for tubercle bacilli.

a large cavity backward so that the thoracoplasty would have a better chance of completely closing it; this expectation was apparently met in all three. The extensive and effective thoracoplasty that is used at present would rarely need the preliminary aid of pneumonolysis.

One of the three remaining patients, for whom the operation was used independently, died as a result of the operation, which was the third death in the whole series of seven operations. The patient was

27 years old; he was fat, was losing weight and had persistent night sweats. On anatomic grounds, a thoracoplasty was indicated but was feared because of doubt about a "fatty heart." Immediately before pneumonolysis, the blood pressure was 104 systolic and 80 diastolic; the pulse rate, 78, and the respiratory rate, 24. Immediately after operation, the blood pressure was 114 systolic and 82 diastolic; the pulse rate, from 126 to 134, and the respiratory rate, 42. The pulse continued to increase in rate and became of poor quality. Five hours after operation the pectoral muscles were removed from beneath the ribs, but without
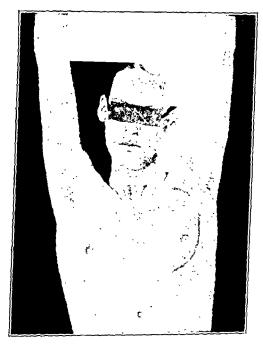
Fig. 7.—Patient whose roentgenograms appear in figure 6, three months after operation.

causing any improvement, and in spite of the administration of oxygen and carbon dioxide, the patient soon died. There was no necropsy.

Another patient for whom the operation was used independently was 56 years old and had arteriosclerosis, intestinal tuberculosis and an anal fistula, dyspnea, hemoptyses, fever and a rapid pulse. He expectorated from 150 to 210 cc. of sputum daily and had had pulmonary tuberculosis for two and a half years. When discharged from the sanatorium seven months after operation, he had gained 20 pounds (9 Kg.), and a roentgenogram showed great clearing in the tuberculous infiltration and apparent disappearance of the cavity; the sputum, however, had been reduced only to 70 cc. daily and was still positive for tubercle bacilli.

The last patient (figs. 6 and 7), 24 years old, had had pulmonary tuberculosis for seven years and had been in sanatoriums on several occasions. He had lost much weight and had expectorated 150 cc. of sputum daily that was positive for tubercle bacilli. Thirteen months after operation he had gained 35 pounds (15.9 Kg.) ; his sputum was reduced to 10 cc. daily and was repeatedly negative for tubercle bacilli during the last four months. This patient presented ideal indications for the operation. Pneumothorax could not be induced because of pleural adhesions. Phrenicectomy alone would almost certainly have been insufficient. Thoracoplasty was contraindicated because of active tuberculosis in the opposite lung. Extrapleural pneumonolysis with paraffin would have been dangerous because the cavities were close to the parietal pleura.

Churchill[8] used supraperiosteal pectoral pneumonolysis for three patients. The results were at first satisfactory but later "not brilliant," probably, he thought, because of muscular atrophy.

SUMMARY

1. Supraperiosteal and subcostal pneumonolysis with a filling of the pectoral muscles is the freeing of the anterolateral portions of the upper ribs from their periosteum and intercostal muscles and the tucking of the pedicled pectoral muscles between the bared ribs externally and the periosteum, intercostal muscles, pleurae and lung internally.

2. The operation is a form of collapse therapy for cavernous tuberculous or nontuberculous pulmonary suppuration. Its indications are much the same as those of the classic extrapleural pneumonolysis, with certain restrictions imposed by the nature of the operation. The indications are relatively few.

3. The supraperiosteal and subcostal placement of the pectoral muscles has important advantages over their placement in a space directly next to the parietal pleura: It is simpler; one runs no risk of tearing the pleurae and lung; the extent of the pulmonary collapse to be produced is readily controllable and is not dependent on the absence of tough extrapleural adhesions; as no rib is resected, the expectorating mechanism is but little interfered with and so the danger of stasis pneumonia is small; the periosteum of the bared ribs is pushed deep into the thorax where it may be expected to form new ribs that will prevent expansion of the lung when the pectoral muscles atrophy.

4. The operative technic is described, and experiences (including Churchill's) with ten cases are given.

8. Churchill, E. D.: The Selection of the Operation for the Patient in Pulmonary Tuberculosis, New England J. Med. **205**:519 (Sept. 10) 1931.

DIURNAL INCONTINENCE IN WOMEN

J. THORNWELL WITHERSPOON, M.A. (Oxon.), M.D.

NEW ORLEANS

There is a type of urinary incontinence in women, termed diurnal incontinence, which usually follows the trauma of childbirth, but which presents no visible injury or infection of the bladder, and has no relation to vesical fistulas. The onset is slow and insidious, the patient rarely being able to determine a definite beginning. The first symptom is the escape of a few drops of urine when the patient coughs, sneezes or makes any sudden movement which increases abdominal pressure. The condition may progress slowly until a continuous leak is present, although occasionally it remains constant; in fact, its limits vary between a slight dribbling on exertion to continuous loss, even when the patient is recumbent. Few infirmities are productive of so much inconvenience, discomfort and mental depression, nor does any other physical disability interfere so completely with the present comfort or future prospects of its victims.

It has always seemed strange that a symptom so distressing as diurnal incontinence should not be mentioned when it is present. However, in older women, especially when the incontinence is only slight, the condition is often ignored, unless specifically asked about. Watson has commented on the absence of complaint of this condition. In 63 cases with cystocele, some degree of incontinence of urine was mentioned in only 19 histories, but when questionnaires were forwarded, 41 additional complaints were obtained. In 183 cases with cystocele, Watson [1] noted urinary incontinence in 120 or 66.1 per cent after detailed questioning concerning this specific symptom. Taylor [2] has even gone so far as to have definite questions regarding incontinence of urine printed in the histories.

Diurnal incontinence should not be confused with frequency of urination, in which there is no wetting of the clothes from urinary dribbling or leakage, but increased frequency in the desire to urinate. Urgency of urination is also different from incontinence or frequency. When the desire to urinate comes, it must be satisfied, even though on

1. Watson, B. P.: Imperfect Urinary Control Following Childbirth, and Its Surgical Treatment, Brit. M. J. 2:566, 1924.

2. Taylor, H. C., and Watt, C. H.: Incontinence of Urine in Women, Surg., Gynec. & Obst. 24:296, 1917.

some occasions the clothes can scarcely be removed in time. Urgent urination often occurs in a normal bladder which is greatly distended, or, as is well known, it may result from a mental association with urination, running water, etc. With increased frequency and urgency, there is always first the desire to urinate, while in incontinence the urine passes without any inclination to urinate or even against voluntary effort to control it. It is well described as a "leaky bladder."

OCCURRENCE

Diurnal incontinence, although it has been observed in nulliparous women, is most common in parous women over 40 years of age (Kelly [3]), and the degree of incontinence is, in general, dependent on the number of children. Taylor and Watt [2] offer the following figures showing its association with an increase in the number of children: 8 per cent with no children, 14 per cent with from 1 to 3 children, 25 per cent with from 4 to 6 children and 29 per cent with from 7 to 9 children.

In some women this condition develops, however, when there is no surgical or obstetric history. It may appear immediately after confinement with instrumental delivery; if it does, as it did in 3 of my cases, rest in bed, hot vaginal douches, daily irrigations of the bladder and the maintenance of an empty bladder, by either frequent catheterizations or an indwelling catheter, will usually result in restoration of normal urinary control.

Contrary to the current belief, diurnal incontinence is not always associated with the more obvious forms of genital displacements, cystocele or prolapse. In fact, in prolapse the retention of urine, the opposite of incontinence, is more often observed. Occasionally the patient actually has to push the cervix upward before she can urinate. The type of incontinence in prolapse, caused by the overflow of retention of urine, has a purely mechanical etiology. Often on superficial examination the vagina, urethra and bladder grossly appear normal. However, if the patient takes a squatting position, and coughs, the typical displacement of the urethra and bladder will take place, which, as described by Bonney,[4] appears as a wheeling of these organs around and under the subpubic angle, until, at the height of the movement, the urethral meatus is directed upward and forward. Bonney claims that it is at this degree of displacement of these organs that the spurt of urine occurs.

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3. Kelly, H. A., and Dumm, W. M.: Incontinence in Women Without Manifest Injury to the Bladder, Surg., Gynec. & Obst. **18**:44, 1914.

4. Bonney, V.: Diurnal Incontinence of Urine in Women, J. Obst. & Gynaec. Brit. Emp. **30**:358, 1923.

DIAGNOSIS

Diagnosis is not always easy. It must be remembered that urinary control in women is less certain than in men. Even with actual evidence of wet clothes, one is often impressed with the difficulty to determine whether the relaxation is due to disturbance of the nerve control to the sphincters, to weakness of the muscles or to their injury. In the nulliparous woman who has never had an operation, it must be assumed that the incontinence is the result of nerve disturbance or of progressive muscular weakness. When passing a catheter or instrument into the bladder, one is often impressed with the lack of sphincteric resistance. This does not necessarily mean lack of sphincteric control, since there exists only a narrow line between a sphincter which will hold water and one which is practically worthless. The slow withdrawal of the Pezzer catheter, until it hangs at the neck of the bladder, is probably the best means of locating the sphincter, while the sound is more convenient to identify an associated cystocele or prolapse.

The endoscope offers a visual method of watching the function of the sphincter while the patient is in the knee-chest position and the bladder is distended with water or air. It will be observed that on withdrawing the endoscope, the vesical sphincter closes over the end of the instrument with its normal tonicity. In diurnal incontinence prompt contraction of the sphincter is not generally observed.

Urinary fistulas, aberrant ureters, cystitis, tabes dorsalis, urethritis, trigonitis, spina bifida, and lesions of the central nervous system must be ruled out as the source of any organic factor in the etiology of diurnal incontinence.

EXPERIMENTATION

Bonney[4] performed the only experimental work in testing the strength of the vesical sphincter or the expulsive power of the bladder that was found described in the literature. Measuring the force exerted with a water manometer attached to a catheter inserted in a partly filled bladder, he told the patient to attempt urination and then to cough. In 6 patients there was marked variation, from 100 to 8 mg. of mercury, in the force exerted, while coughing produced only an additional rise of 12 mg. in the 3 patients examined. The catheter was again introduced only as far as the external urethral meatus of an empty bladder, while the water head pressure was raised to sufficient force to overcome the sphincteric contraction and pass into the bladder. In 5 of the 6 patients examined in sitting positions the expulsive force of the bladder was greater than the pressure required to dilate the sphincter from below. In general, Bonney's conclusions were that the escape of urine on coughing in diurnal incontinence is not, or is only partially, due to the intra-

vesical pressure overcoming the sphincter muscle; it is due rather to some interference with the intrinsic sphincteric mechanism. He suggests, however, that his experiments are too few to allow him to dogmatize.

<div align="center">ANATOMY</div>

General anatomic descriptions of the bladder vary between excess of detail, which is monotonous and confusing, and broad statements, which tend toward anatomic inaccuracy. For the sake of clarity, the anatomy of the female bladder is outlined under three headings: the bladder proper, the vesical supports and the sphincteric control of the bladder. The bladder can be described as having a mobile portion, its wall, which distends and contracts according to the contents, and a fixed or immobile part, the trigone, which represents a place of entrance of the ureters, of exit of the urethra and of juncture of the muscle walls of the bladder looping around the vesicle neck and upper part of the urethra. It is only this fixed part, the trigone and base of the bladder, with which I am concerned, since, as I shall attempt to show, any relaxation or weakness of this part will give rise to the type of incontinence under discussion.

The most anterior portion of the bladder and trigone rests on a deep facial sheath which is attached to the posterior aspect of the pubic bone and to the under surface of the fascia of the rectus and pyramidalis muscles. If this union is divided when a low, midline incision is made, the bladder tends to fall backward, and because of this I make it a point, after this type of incision, to anchor, by a special stitch, the bladder and its peritoneal fold to its original attachment. This sheath runs posteriorly in a horizontal manner, then angulates itself upward to be attached to the cervix. The lateral attachment of this sheathlike structure is the levator ani muscles and the parametric tissues. Hence it is readily seen that the vesical trigone is strongly attached anteriorly, and thus assures itself of excellent support, while posteriorly the angulated part of the fibromuscular sheath is weak, and its attachment to the cervix, a movable organ, does not assure this posterior part of the trigone and urethra the same support of fixation as noted anteriorly. I stress the weakness of the trigone posteriorly and its strength anteriorly as the main source of diurnal incontinence. The fascial planes of cleavage of this sheath are made use of when the bladder is separated from the anterior vaginal structures in the performance of an abdominal panhysterectomy and in vaginal operations requiring separation of the bladder from the anterior vaginal wall.

It is believed that there are two urinary sphincters in a woman, the vesical and the urethral. The former is composed of the smooth muscles of the bladder wall, as shown by the blending of the bladder mucosa with the vesical structures. Its control is involuntary. However, there

is some doubt as to its real existence and functions, as has been shown by dissection (Grimsdale). The urethral sphincter, the external sphincter, composed of striped or voluntarily controlled muscle, is formed of the circulatory fibers of the perineal muscles lying in the musculo-fascial sheath already described, and is closely associated with the fibers of the urethral compressor muscle. In fact, nowhere along the urethral tract are the walls of the urethra thicker than they are at this location, being situated between the fascial planes which support the trigone. It is a distinct muscular structure, and since it is so firmly embedded in the fixed trigonal supports arising from the pubis, I feel that its sphincteric powers are one of the main controls of the act of micturition, and that its proper functioning will prevent diurnal incontinence.

The nerve supply to the bladder is from two sources: 1. The fibers of the second, third and fourth sacral roots maintain voluntary control. 2. These fibers mingle with the sympathetic innervation in the superior and inferior hypogastric plexuses, which is the source of involuntary vesical control; the nerve fibers from both sources descend along the ureters and vesical blood vessels to reach their destination.

MICTURITION REFLEX

Before investigating the sphincteric mechanism in diurnal incontinence, the normal physiology of urination and the micturition reflex should be examined, since I consider micturition such a complex act that any fault in its mechanics might be more important than an anatomic defect. The act of micturition is performed through the reciprocal stimulation and inhibition of the vesical sphincters and the bladder musculature, aided by voluntary increase of intra-abdominal pressure. That there is a voluntary and involuntary control over emptying the bladder is attested not only in the conscious and unconscious states of being, but also by the infant's reflex response to its first desire to urinate. Later these first demands to urinate are resisted through voluntary control through the higher nerve centers. Some recent work suggests an intrinsic or automatic nerve mechanism within the bladder walls.

I should like to stress the complexity of this reflex of micturition. No matter what might be the causative mechanism at the onset of micturition, once urine begins to pass the sphincteric levels, the immediate cessation of urination is difficult, since the sphincteric control is reflexly inhibited. In this difficulty lies a possible explanation of the unpleasant wetting of the clothes in diurnal incontinence.

MECHANISM

Many theories of the mechanism causing diurnal incontinence are offered. One example is Bonney's[4] description of the laxity of the

anterior part of the musculofascial sheath, so that it yields to sudden pressure and allows the bladder to slip behind the symphysis pubis and the urethra to fall downward and forward by wheeling round under the pubic arc. Bonney, however, offers no explanation of a similar displacement of these organs without incontinence. I cannot agree with Bonney's idea of the existence of a valvular mechanism at the angle of the movable bladder and fixed urethra; no similar mechanical arrangement is found at the orifice of any other meatus when relaxation occurs.

Young [5] is of the opinion that no incontinence can exist as long as the external or voluntary sphincter is intact, and that incontinence can occur, as noted by this author, only when sphincteric power is lost. Dougal [6] supports Young's theory and adds evidence to this hypothesis by noting the maintenance of urinary control in prolapse. Watson [1] conforms to a similar belief of the importance of the external sphincteric control. Stoeckel may be correct in emphasizing the importance of obstetric lacerations to the internal sphincter, with resulting restricting adhesions, but the importance of this is doubtful because of the indifferent sphincteric findings on the cadavers of Grimsdale, and also because obstetric maneuvers tend to elevate and push forward the bladder base under the pubis rather than to tear through it. However, the possibility of damage to innervation of this sphincter from obstetric injuries is not to be overlooked.

I believe that weakness of the natural fixation of the vesical base is an all-important cause in the mechanism of diurnal incontinence. The neck of the bladder and upper part of the urethra are attached anteriorly to the symphysis pubis by comparatively strong fibrous bands, while posteriorly they are incorporated only with the anterior vaginal wall, which is prone to become displaced as a result of obstetric injuries. Relaxation of the inferior neck of the bladder and posterior urethra drags on the anterior vesical supports and forms a type of suspensory ligament which causes a funnel-shaped orifice to occur at the internal urethral meatus. With such a funnel-shaped relaxation of the internal sphincter (ready to pass urine) and with the associated complex micturition reflex (when once urine is allowed to pass the urethral sphincter more urine flows freely), it is easy to conceive that incontinence would be the result of sudden abdominal strain, even though no cystocele were present. When the latter condition exists, even in the absence of incontinence, the musculofascial sheath retains its tension in the region of the

5. Young, E. L.: Urinary Incontinence in the Female, J. A. M. A. **79**:1753 (Nov. 18) 1922.

6. Dougal, D.: Urinary Incontinence in Women, with Special Reference to the Operative Treatment in Young Nulliparae, J. Obst. & Gynaec. Brit. Emp. **31**: 46, 1924.

neck of the bladder and urethra, both posteriorly and anteriorly, but it is weakened over that portion of itself which is angulated on the anterior vaginal wall and which ultimately is inserted into the cervix. I contend, therefore, that the damage causing incontinence alone and that causing cystocele alone occur at different places. The former is definitely associated with weakness of the posterior aspect of the neck of the bladder and the urethra, with the anterior attachments to the pubis remaining intact and thus supporting the base of the bladder by the anterior wall of the sphincter; while true cystocele is a bladder hernia, protruding between the edges of the separated fascial layer
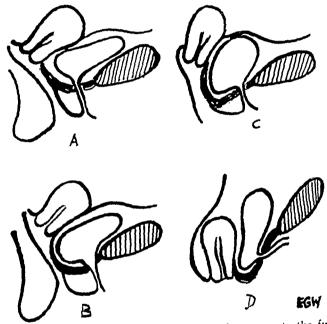
Fig. 1.—*A*, normal bladder. *B*, associated incontinence; note the funnel-shaped orifice at the internal urethral meatus. *C*, cystocele; the bladder is torn from its pubic attachment and sags posteriorly, but there is no drag on the urethra. *D*, prolapse; the part of the bladder below the urethra often retains urine after voiding.

supports, and therefore not necessarily associated with damage of the sphincter.

In addition to the sphincteric weakness, I consider the tonicity and strength of the vaginal walls as important factors in the production of diurnal incontinence. Complete relaxation of the posterior and anterior vaginal walls will eventually result in procidentia, while relaxation of these walls in various degrees usually gives rise to rectocele or cystocele alone or in combination. If, however, only the anterior wall is weakened from obstetric injuries, and the pelvic floor maintains its normal support, the cervix will push downward in a piston fashion if there is a sudden increase of abdominal tension. The only outlet for such a

· force is on the weakened anterior vaginal wall, tending to drag the posterior aspect of the base of the bladder and the urethral neck with it, since the perineal floor posteriorly maintains sufficient strength to direct forward and anteriorly the plunging action of the cervix.

That such obstetric injuries can occur only to the anterior vaginal wall, while the perineal floor remains comparatively normal, is often seen in the narrowed angle type of pelvis, in which episiotomy is common and too frequently the oncoming head is pushed forward to "save the perineal floor." Also, the long tedious labors of women with this type of pelvis, compared to the easy delivery of women with a broad-angled pelvis, tend to increase injuries to the anterior vaginal wall. Watson [1] suggested early prophylactic episiotomies in the narrowed arch pelves as preventatives to subsequent diurnal incontinence.

Van Duzen [7] dissected the trigonal and urethral tracts of cadavers. He found that injuries to the trigonal muscle and separation of it from the underlying fascial sheaths posteriorly produce cystocele. He obtained several bladders from women who died shortly after their first delivery, and in all those examined there was only partial division of the inter-ureteric muscle, whereas in cadavers of multiparous women, the entire trigonal muscle was often atrophied, attenuated or even absent. In cadavers of younger women this important muscle was partially destroyed in all cases after a sufficient lapse of time since the last delivery. His natural conclusions were that repair work from obstetric injuries on the anterior vaginal wall should be performed as early as possible.

Undoubtedly, local pelvic injury at the time of parturition is considered the most important single cause of this deplorable condition, and, because of the unfortunate results following delayed repairs after confinement, I strongly advocate immediate operation on the posterior vaginal wall and repair of the anterior wall as soon as involution has taken place. In fact, this is a point that one cannot overemphasize. Too often I have seen complete tears into the rectum or vesical-vaginal fistulas develop from only partial damage to these parts; but if infection sets in untoward results usually follow, or else the irregular scar formation gives rise to local pelvic pain or often to abnormal functioning of the organs involved.

TREATMENT

As stated by Young,[5] "The records of attempts to cure urinary incontinence in the female are interesting illustrations of the inability of most men to go straight to the point in working on any problem involving a part of the human body." The history of the various

7. Van Duzen, R. E.: The Use of the Cystoscope as a Control in the Diagnosis and Treatment of Cystoceles, Urol. & Cutan. Rev. 36:187, 1932.

phases of treatment offers many methods, of which the majority are · more or less futile, many ridiculous, and some even dangerous. Contractile collodion has been painted over the internal meatus, radical cauterization of the urethra has been used, and even paraffin has been injected under the mucosa to insure permanent pressure around the lumen of the urethra. Silk stitches have been placed around the urethra to form an artificial sphincter. Hydrotherapy, in the form of hot or cold footbaths and douches, has proved of no avail. Lumbar puncture and injections into the sacral nerve roots have been tried in the hope of stimulating sphincteric action. Tampons and pessaries locally placed have always failed, as have drugs. Pressure bandages, dieting, hygienic measures, counterirritants by means of blister formation and electricity have been employed. Permanent artificial channels to the bladder have been opened from various locations. Advancement of the urethra, by a method described by Pawlick and improved by Dudley, resulted in 4 of 5 cures by the latter author. Frank described partial resection of the urethral wall to lessen the circumference of the lumen, while Gersuny, Pousson and Ries have twisted the urethra and then resutured it in its original location. Transplantation of muscles to form new sphincters has been devised; Goebel's technic, improved by Stoeckel, makes use of strips of muscle from the pyramidalis, bringing them downward posterior to the symphysis. Taussig[8] has employed the levator ani muscles, Deming[9] the gracilis and Novwy the adductor magnus and biceps femoris to perform the same function. H. H. Young[10] employs both the suprapubic and the perineal approaches in males, but I am inclined to believe that suprapubic drainage should be reserved for cases in which the vaginal route is technically too difficult, that is, when the vagina is very small, senile or atrophic, as scar tissue is often present around the base of the bladder.

In 1914 Kelly reported 20 cases with 16 cures in which the neck of the bladder was plicated with a mattress suture of fine linen. Since this report, other gynecologists have employed Kelly's technic with minor variations. E. L. Young[5] advocated the isolation by dissection of the torn external ends of the sphincter, and their resuture: plication of the vesical neck is thought to be only secondary in importance. He cured 18 patients, 100 per cent, by this technic. He described the ease with which these torn ends of the sphincter can be isolated and

8. Taussig, F. J.: A New Operation for Urinary Incontinence in Woman by Transposing Levator Ani Muscles, Am. J. Obst. & Gynec. **77**:881, 1918.

9. Deming, C. L.: Transplantation of Gracilis Muscle for Incontinence of Urine, J. A. M. A. **86**:822 (March 20) 1926.

10. Young, H. H.: Operation for the Cure of Urinary Incontinence, Surg., Gynec. & Obst. **28**:84, 1919.

defined, although in my own experience, I find their isolation next to impossible, and often hesitate to search for them for fear of destroying adjacent tissue which is helpful in sphincteric approximation from fascial support.

Bonney's original treatment, supported by Berkeley, of tautening the vesical sphincter seems rather practical, but now these authorities are of the opinion that the only important consideration is strengthening the anterior portion of the fibromuscular sheath. They consider the overfolding of the periurethral tissue to be far less important at present, since their belief is that true diurnal incontinence is the result of relaxation of the anterior portion of the musculofascial sheath, and, in consequence, the only cure of this malady is the tightening of this weakened support anteriorly.

The operative technic which I have followed is similar to that advocated by Kelly. With the patient in the lithotomy position, an annular
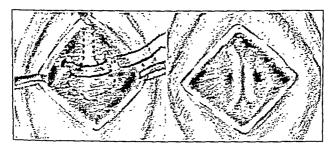
Fig. 2.—Method of insertion of mattress suture at the bladder neck. The first suture is tied.

incision is made around the anterior lip of the cervix at its vaginal junction, and a median incision is carried anteriorly at right angles toward the external urethral orifice. The anterior vaginal structures are separated from the bladder sufficiently posteriorly to expose the bladder base and upper urethral neck, the locations of which can be determined by palpation with the use of a Pezzer catheter inserted in the bladder. By gentle traction on the catheter, and with one finger against the urethral neck, the location of the sphincter is noted as the structure just anterior to the "point of hang" of the catheter on its withdrawal. The actual determination of the location of the external sphincter is essential to insure good postoperative results and to prevent urethral injuries. I do not try, however, to isolate the torn ends of the sphincter, since, as I said before, too much dissection in this region may result in increased destruction of sphincteric tissue, or penetration into the bladder and urethra. I exercise great caution in operating on elderly women whose sphincteric muscle is mainly fibrous tissue, and consequently more

difficult to find and easier to destroy. The aim of the operation is to insert two tiers of mattress sutures so as to include and imbricate on themselves the tissues of, and adjacent to, the neck of the bladder, the sphincter muscle and the posterior urethra, so that these surrounding fibromuscular tissues are enfolded on themselves against the floor of the posterior urethra. In consequence, the urethral lumen is narrowed from side to side at this point. The adjacent tissues are sufficiently secured so that a fixed "point d'appui" is reestablished from which the sphincter can act. Indeed, if one plicates where one thinks the neck of the bladder ought to be, and restores it to its normal location, the resulting cure of incontinence is usually obtained. No undue tension should be made on the sutures, as sloughing may result. An important stitch is the suture on the neck of the bladder to insure additional narrowing of the urethral orifice superior to the sphincter; but the exact location of this suture is not always easy. I make a point of saving as much as possible of the musculofascial sheath, and imbricate it on itself. Only the vaginal mucosal edges are trimmed.

If more extensive injuries, as cystocele, are associated, it is as necessary to repair the sphincteric control as it is to reestablish the normal position of the bladder. Unfortunately, this is a fact frequently neglected and is usually responsible for the persistence of incontinence after the usual type of anterior colporrhaphy. In the combined condition of incontinence and cystocele, in addition to plication of the bladder and urethral neck, I imbricate the remnants of the overlying fascia all the way down to the cervix in order to assure additional vesical support.

The Watkins interposition operation is well chosen in cases of cystocele and prolapse associated with incontinence, in which the senile atrophy of the musculofascial sheath makes its separation from the vaginal mucosa and bladder a difficult procedure. This operation is especially helpful in large, flaccid atonic bladders. A perineorrhaphy in combination with any of the operations mentioned is most important, but such additional support is not always offered. Restoration of all the injured pelvic parts as nearly as possible to their original appearance is the ideal, and so additional support from a repaired pelvic floor tends to relieve part of the strain that otherwise would be borne by the anterior vaginal wall.

Too often the repaired perineum is asked to supply more than its share of support, in fact the whole support, and I cannot condemn too strongly the simple perineorrhaphy, done all too frequently, to cure incontinence. Such operative procedure is only short of a criminal act and has its foundations built on anatomic ignorance, surgical inability and poor judgment.

In associated fibromyomatous growths, any drag by the tumor through the anterior vaginal wall on the sphincteric control should be relieved if the incontinence is expected to be cured.

The effect of subsequent pregnancy and confinement on the permanence of urinary control following incontinence, once it has been established by surgical means, is still an open question, and my experience has been too limited to offer any definite results.

In the rare case in which the operative risk is too great to offer surgical aid, I use a soft ring pessary which I find more helpful than any other procedure. This support is inadequate, but fortunately such cases are rare, and the use of the pessary is correspondingly infrequent.

POSTOPERATIVE CARE

The most important postoperative care is avoidance of infection and overdistention of the bladder. The choice of methods for such treatment is insertion of an indwelling catheter at the time of operation or frequent catheterizations, every six or eight hours postoperatively. I prefer the former, and leave the catheter in place for from six to eight days, since I find less infection and quieter convalescence with this method. After the fifth day, if all is going well, I frequently have the catheter clamped intermittently in order to permit the bladder to accustom itself to its future work, so to speak. It is wise to catheterize the patient after her first normal voiding to insure that there is not too great a residuum of urine, possibly caused by a too snug suture. A small amount of residual urine often occurs, which usually disappears within a week.

Many authorities favor frequent catheterizations over the indwelling catheter. Results reported in the literature do not offer evidence definite enough to substantiate one method in favor of the other. However, I am inclined to feel that the nursing care is an important feature in either method. If the indwelling catheter is allowed to become dirty or plugged so as to obstruct the urinary flow, ideal results are not obtainable; whereas if frequent catheterizations are performed indifferently, so as to stretch the newly sutured sphincteric area, or if they are performed without strict aseptic precautions, untoward results may follow.

CURES

The cures resulting from the different types of operations vary between wide limits; Watson [1] reported 66 per cent cures in 105 cases; Kelly, 80 per cent in 20 cases, Furniss,[11] 80 per cent in 21 cases, and

11. Furniss, H. D.: Urinary Incontinence in Women, S. Clin. North America 5:249, 1922.

E. L. Young,[5] 100 per cent in 18 cases. My own statistics, based on thirty-four cases of multiparous women, are offered in the following table:

Data in Author's Cases

	Years
Age	
Oldest	65
Average	42.6
Youngest	25
Instrumental deliveries	11 (33%)
Associated cystocele	15 (44%)
Associated rectocele	16 (47%)
Types of operations	
Kelly technic	29
Perineorrhaphy	25
Vaginal hysterectomy	3
Watkin's interposition	2
Repair of complete tear	1
Results	
Cured	14
Improved	5
Unimproved	2
Undetermined	13

CONCLUSIONS

Diurnal incontinence is a most distressing condition, and in view of the fact that the operation advocated for the cure of this discomfort is not difficult, the extent to which its use has been neglected is amazing. Some of the most grateful patients are those who have been helped by operation. In the majority of cases of urinary incontinence, especially in multiparous women, the condition can be cured or, at any rate, relieved by operation. Undoubtedly many single women are allowed to go on suffering from this ailment because no obvious lesion can be found, and the disability is attributed to a neurosis. A neurotic element is present in some cases, especially in the nulliparous girl, in whom urinary control is sensitive to nerve influence; but the real cause usually lies in the weakness of the sphincteric mechanism, which can be dealt with successfully by the surgical methods advocated in this paper.

1640 Arabella Street.

AVULSION OF THE EPIPHYSIS OF THE SMALL TROCHANTER

DON KING, M.D.

ANN ARBOR, MICH.

Isolated avulsion of the small trochanter is uncommon, only sixty-one cases having been reported in the literature. I have recently observed a case, and wish to report it, in conjunction with the essential facts derived from a study of the sixty-one previously reported cases.

REPORT OF A CASE

History.—A colored boy, aged 14 years, came to the clinic on June 8, 1932, complaining of pain in the upper medial third of the right thigh and stiffness of the right hip. He stated that the day before, during a ball game, he had made a quick stop on approaching a base. As he did this, the trunk was suddenly hyper-extended on the lower extremities. He felt something give way in the right thigh; this was accompanied by sharp pain and a fall to the ground. He had to be helped to his feet but found that he could walk unaided by "holding the hip stiff." This could not be accomplished, however, without considerable pain. On reaching home, he immediately went to bed. There was no pain when he was lying quiet with the hip flexed. The following morning he was able to get up and walk to the clinic.

Examination.—Station and Gait: When the patient was standing, the weight was carried mainly on the left leg, the right knee and hip being held in slight flexion. In walking, the right hip was held rigid, and the trunk was bent forward at the hips.

Supine Position: The right hip was held in 30 degrees of flexion. There was no visible swelling, ecchymosis or deformity due to external rotation. There was severe tenderness to pressure over the small trochanter in the upper third of the mesial aspect of the thigh, but there was no shortening of the extremity, and manipulation elicited no crepitus. A full range of flexion and rotation at the hip joint could be elicited passively, if great care was used in the manipulation. The movements of abduction and extension were limited by pain and spasm in the muscles. The patient could actively flex the thigh while lying on his back, but not while seated on the edge of the table with the legs hanging over the side (Ludloff's sign). The clinical diagnosis of avulsion of the small trochanter was confirmed by the roentgenogram (figure).

Treatment.—On the day of admission (June 8, 1932) a hip spica was applied, with the affected thigh in a position of 45 degrees of flexion and mild abduction. After three weeks the cast was removed, and brine baths were started. These were given for four days, following which the patient was allowed to walk. There

was a mild limp for a week, but when the patient was last seen (Aug. 18, 1932), nine weeks after the injury, the gait was normal, and the clinical examination showed nothing of note.

ANATOMY

The psoas major muscle arises from the transverse processes and the lateral surfaces of the bodies and disks of the five lumbar vertebrae. The iliacus muscle arises from the iliac crest, from the anterolateral portion of the anterior surface of the sacrum and from the greater portion of the iliac fossa. From these extensive areas of origin the fibers of the two muscles converge downward, forward and lateralward to a small area of insertion on the small trochanter and on the surface of the femur immediately distal to the trochanter. Flexion at the hip joints is produced by the iliopsoas muscles. When the trunk is fixed, contraction

A shows typical upward and medial displacement of the avulsed epiphysis. In *B*, taken five weeks after the accident, the epiphysis is firmly united to the shaft.

of the iliopsoas muscles flexes the thighs, and when the thighs are fixed, their contraction flexes the trunk. The power required to effect these movements is considerable, and hence the pull on the small trochanter must at times be very great.

The center of ossification for the small trochanter appears at about the twelfth year of age and unites with the shaft at about the eighteenth year.

ETIOLOGY AND PATHOLOGY

Predisposing and Immediate Causes.—Isolated fracture of the small trochanter occurs almost exclusively in boys between the ages of 13 and 17 (table 1). The right thigh is almost twice as commonly affected as the left. The fracture often occurs in athletic activities. When a person runs or makes a sudden stop while running, the pull on the epiphysis from contraction of the iliopsoas muscles is so great that the

small trochanter is at times avulsed. The fracture is also often produced as follows: Sometimes, while standing or running, a boy loses his balance, and in order to restore equilibrium, he suddenly hyperextends the trunk on the thighs, thus avulsing the trochanter.

Owing to the depth of the overlying soft tissues, and to the situation of the trochanter on the internal aspect of the upper part of the femur,

TABLE 1.—*Incidence of Avulsion of the Epiphysis of the Small Trochanter*

Sex		Age		Side Affected	
Males	59	Number of cases given	56	Right	33
Females	2	Youngest	8 years	Left	19
Unknown	1	Oldest	87 years	Not given	10
Total	62	Average	19 years	Total	62

Forty-Two of the 56 Patients Were Between 13 and 17 Years of Age, as Follows:

Age	Number of Cases
13	6
14	11
15	11
16	6
17	8
Total	42

TABLE 2.—*Summary of the Methods of Treatment and of the End-Results in 50 Cases*

Number of patients on whom I have data as to the end-results of treatment	50
Number of patients who completely recovered	46
Number of patients who died during treatment	4*
Treatment employed to secure the high percentage of cures (46 of 50 = 92%)	
Traction and rest in bed	5
Rest in bed with sandbags to hold the hip in flexion	14
Hip spica with hip in flexion (varying degrees of abduction or adduction)	19
Operation (wiring epiphysis to shaft)	1
Adhesive strapping	1
Rest in bed only	3
Rest in bed with limb immobilized in flexion in Thomas splint	1
No treatment	2
Total	46

* The four patients who died were: (1) a greatly debilitated man, aged 82, who entered the hospital fourteen days after injury and died on the same day (Juillard, 1879); (2) a boy, aged 19 years, who died of sepsis after receiving some "hard kicks in the buttocks"; autopsy revealed separation of the trochanter (probably pathologic), complicated by infected hematoma and pericarditis (Brunelle, 1854); (3) a boy, aged 17 years, who died of septicemia fourteen days after operation (Fenwick; reported by Hutchinson, according to Ross); (4) a child, aged 8 years, observed by Carthy; the case was cited by Ruhl, but no further details were given.

fracture by direct violence does not occur. For the same reason, the fracture is always a simple one. Several cases produced by indirect force have, however, been recorded. Hoch's [1] patient was struck by a falling chimney piece, while the patients of Naegeli,[2] Peggar,[3] Gray [4]

1. Hoch: Ztschr. f. Chir. **97**:405, 1909.
2. Naegeli: Beitr. z. klin. Chir. **77**:242, 1912.
3. Peggar: Beitr. z. klin. Chir. **81**:138, 1912.
4. Gray: J. Roy. Army M. Corps **18**:578, 1912.

and Heath [5] sustained the fracture by falling with the full weight on the hip.

Pathology.—A large majority of the reported cases of isolated fracture of the small trochanter are in reality cases of epiphyseal separation. The. epiphyseal displacement is always in the same direction, upward and medialward, toward the adductor region. In older people, in whom the epiphysis is firmly fused, the trochanter is torn from the shaft, carrying with it a piece of the femoral cortex (six of fifty-nine cases). In such instances the trochanter is occasionally broken into several pieces.

<div align="center">DIAGNOSIS AND TREATMENT</div>

Symptoms and Signs.—When a person is running, suddenly stopping or attempting to restore a lost equilibrium he feels a sharp, severe pain in the upper medial third of the thigh. A feeling of something tearing is not uncommon. The patient often falls to the ground but usually can arise and, by "holding the hip stiff," walk unaided. Some of these patients have been able to walk backward better than forward. As the insertion of the hip-flexor muscle is incompletely torn away, the result is partial or complete disability of the hip-flexor mechanism. There is a loss of ability to flex the thigh actively when the patient is seated on the edge of a table, but when he is lying supine, active flexion of the thigh is possible because of the quadriceps extensor mechanism. This sign (Ludloff) is present in a high percentage of cases and can be considered diagnostic. Flexion deformity of the hip is commonly present, but there is no true shortening, and ordinarily there. is no visible ecchymosis. A hematoma is often deeply palpable on the medial aspect of the upper part of the thigh, and tenderness to pressure is marked over the small trochanter. If the thigh is moved slowly and handled gently, the full range of flexion and rotation at the hip joint can be obtained, but abduction and extension are limited by spasm and pain in the muscles.

Differential Diagnosis.—The age of the patient and the absence of deformity due to external rotation, crepitus and shortening serve to differentiate this lesion from fracture of the femoral neck. A contusion of the soft tissues in this region is differentiated by the history of direct trauma, by the presence of a full range of motion in the hip joint and by the absence of the Ludloff sign.

Prognosis and Treatment.—The end-result is given in the histories of fifty of the sixty-one cases reported in the literature. Forty-six of this number are credited with a perfect result. The different methods of treatment employed to obtain this result vary from no treatment

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5. Heath, O.: Proc. Roy. Soc. Med. (Sect. Orthop.) **16:**12, 1923.

(two cases) to open reduction (one case), and are listed in table 2. This table shows that the avulsed epiphysis will heal, no matter what form of treatment is used. Even though roentgenograms reveal the fragment considerably displaced, the intervening space between the shaft and the trochanter always fills in with callus, and a perfect union results.

COMMENT

I think that the most logical method of treatment is fixation of the affected thigh in 45 degrees of flexion by a hip spica. This position approximates the fragments and relaxes the iliopsoas muscle. I believe that the cast should extend to just below the knee, with the extremity neutral as to rotation and abduction. After three weeks of immobilization, union is firm and bearing of the full weight may be rapidly accomplished.

SUMMARY .

1. Isolated fracture of the minor trochanter is uncommon, my case being the sixty-second to be reported.

2. In practically all cases, it is an avulsion of the epiphysis. It occurs almost exclusively in boys between the ages of 12 and 18, the time during which the epiphysis develops.

3. It might well be termed a "sport injury."

4. Diagnosis can be made on the basis of the history and the physical findings. An important sign is the patient's inability to flex the thigh actively when he is seated on the edge of a table, although there is retention of active flexion when he is supine (Ludloff's sign).

5. The characteristic displacement of the avulsed epiphysis is upward and medialward.

6. Perfect healing with no loss of function was reported in 92 per cent of a series of fifty instances collected from the literature. A wide variety of methods of treatment were used.

7. Treatment consists in three weeks of immobilization of the thigh in flexion, preferably in a plaster cast.

8. No further manipulation or operation is indicated, even though in the roentgenogram the epiphysis appears rather widely separated from the shaft.

INTRAMURAL EXTENSION OF GASTRIC CARCINOMA

ADRIEN VERBRUGGHEN, M.B., Ch.M., M.S.

CHICAGO

When performing extensive resections for carcinoma of the stomach, one of the most important considerations is to resect clear of the growth.

In this paper it is proposed to show how a general estimate can be made of the probable extension of any given carcinoma into and through the gastric wall. The problem must have presented itself first to Billroth, the originator of resection of the stomach, for Guinard[1] quoted von Eiselsberg as saying that in Billroth's clinic the resected portion extended several centimeters beyond the growth. Mikulicz[2] advocated removal of from 5 to 10 mm. of duodenum and from 5 to 10 cm. of apparently healthy stomach, but in a well defined tumor he thought that removal of from 1 to 2 cm. of apparently healthy stomach was sufficient. Czerny[3] was more moderate, and advocated removal of 3 cm. of apparently healthy tissue. Guinard himself thought that in well circumscribed tumors the resected portion should include 2 or 3 cm. of healthy stomach, but that in the infiltrating type of tumor practically the whole viscus should be removed.

In 1900 Cunéo[4] made the first extensive study of the manner of invasion of the wall by carcinoma of the stomach. He noted that the submucosa is invaded early, that it is invaded to a greater extent than the mucosa, and that at still greater distance from the tumor there are carcinomatous lymphatic structures which cannot be detected except by the microscope. He reported the general tendency of carcinoma of the stomach to spread toward the lesser curvature and to involve the various

1. Guinard, U.: La cure chirurgicale du cancer de l'estomac, Paris, G. Steinheil, 1898.

2. Mikulicz, J.: Beiträge zur Technik der Operation des Magencarcinoms, Arch. f. klin. Chir. **57**:523, 1898.

3. Czerny, quoted by Guinard,[1] and by Carle, A., and Fantino, G.: Beiträge zur Pathologie und Therapie des Magens, Arch. f. klin. Chir. **56**:217, 1898.

4. Cunéo, Bernard: Note sur quelques points de l'anatomie pathologique du cancer de l'estomac, Rev. de chir., Paris **21**:513, 1900; De l'envahissement du système lymphatique dans le cancer de l'estomac et de ses conséquences chirurgicales, Paris, G. Steinheil, 1900, p. 34. Cunéo, Bernard, and Delamere, Gabriel: Les lymphatiques de l'estomac (étude anatomique et histologique), J. de l'anat. et physiol. **36**:393, 1900.

groups of lymph nodes. He also recognized that the mucosa of the stomach passed through a polyadenomatous stage to carcinoma; and in this respect, his paper supports the later contentions of MacCarty [5] and of Cheatle.[6]

There is no later paper on the spread of carcinoma in the stomach than that of Cunéo; however, similar studies of the breast have been carried on by Handley [7] and by Cheatle,[6] and on the rectum by Handley,[8] Cheatle [9] and Cole.[10]

I took up the problem in the same manner as Cunéo, and my work was near completion before I read his paper. However, I hope to confirm and to extend his observations. Recent suggestions in regard to the grading of carcinoma and to the manner of its extension in the face of fibrosis and lymphocytosis reveal some interesting facts when applied to a study of the extension of carcinoma of the stomach.

MATERIAL AND METHOD

The fifty specimens used in this study were removed at the Mayo Clinic between January, 1927, and May, 1928. The cases were taken in rotation except when, for some reason, the specimen was unsuitable for study. Certain specimens had been cut so that they were unsuitable, and others had been utilized by fellow investigators. The type of material used can be seen by reference to table 1. The preoperative diagnosis follows: gastric carcinoma, forty cases; gastric ulcer, three; multiple polyps, two; obstructive lesions, two; benign tumor of the stomach, one; deformity of the stomach, one, and pyloric lesion, one.

Each specimen was subjected to the following examination and procedure:

Macroscopic Examination and Description.—The result of this examination will be seen in table 1. The presence or absence of involvement of nodes was noted at this examination, which is the routine adopted in handling all specimens surgically removed at the Mayo Clinic.

Cutting of Block from Tumor on Lesser Curvature.—The blocks were cut from this part of the stomach for two reasons: First, it is in this situation that the surgeon finds most difficulty in obtaining sufficient healthy tissue for his resections, and at this spot the line of resection passes closest to the tumor, and conse-

5. MacCarty, W. C., and Mahle, A. E.: Relation of Differentiation and Lymphocytic Infiltration to Postoperative Longevity in Gastric Carcinoma, J. Lab. & Clin. Med. **6**:473 (June) 1921.

6. Cheatle, G. L.: Desquamative and Dysgenetic Epithelial Hyperplasias in the Breast, Brit. J. Surg. **13**:509 (Jan.) 1926.

7. Handley, W. S.: The Surgery of the Lymphatic System, Brit. M. J. **1**:922 (April 16) 1910.

8. Handley, W. S.: Recent Advances in the Surgical Treatment of Some Forms of Cancer, Univ. M. Rec., London **1**:385 (May) 1922.

9. Cheatle, G. L.: The Spread of Cancer in the Lower Part of the Large Intestine, Brit. M. J. **1**:303 (Feb. 7) 1914.

10. Cole, P. P.: The Intramural Spread of Rectal Carcinoma, Brit. M. J. **1**:431 (March 1) 1913.

TABLE 1.—Summary of Material

Case	Description of the Pathologic Condition	Involvement of Lymph Nodes	Plane of Maximal Extension	Classification by Extension	Broders' Grading	Distance of Lateral Extension
1	14 cm. stomach and duodenum; adenocarcinoma (8 by 4 by 1.5 cm.) with nodes inflammatory; endothelial hyperplasia	—	Submucosa	II	2	
2	14 cm. stomach; carcinoma (4 by 5 by 2 cm.)	—	Submucosa	III	4	10 mm.
3	Carcinoma, grade 4 (6 by 6 by 3 cm.) with involvement of serosa	+	Submucosa	IV	4	30 mm.
4	11 cm. stomach; adenocarcinoma (7 by 5 by 2 cm.)	+	Submucosa, serosa	III	3	8 mm.
5	12 cm. stomach; adenocolloid carcinoma (6 by 5 by 1.5 cm.)	+	Submucosa	III	3	No distinct edge
6	13 cm. stomach; adenocarcinoma (4 by 4 by 1 cm.) with one node involved	+	Submucosa	II+	3	No extension
7	13 cm. stomach; small cell carcinoma (9 by 7 by 1.5 cm.)	—	Submucosa	II	4	No extension
8	15 cm. stomach; carcinoma (8 by 7 by 1.5 cm.)	+	Submucosa	III	4	At least 5 mm.; not clear
9	10 cm. stomach; adenocolloid carcinoma (5 by 6 by 2 cm.)	+	Submucosa	II	2	No extension
10	7 cm. stomach; carcinoma (5 by 5 by 1 cm.)	+	Submucosa	II	3	No extension
11	10 cm. stomach; carcinoma (5 by 5 by 3 cm.)	+	Mucosa	II	2	No extension
12	10 cm. stomach; carcinoma (2.5 by 2.5 by 1 cm.); involvement of serosa	—	Submucosa	III	3	6 mm.
13	9 cm. stomach; carcinoma (7 by 4 by 2 cm.); involvement of serosa	+	Submucosa	III	3	11 mm.
14	10 cm. stomach; carcinoma (6 by 6 by 1.5 cm.)	+	Mucosa	IV	4	Not clear; at least 5 mm.
15	10 cm. stomach; adenocolloid carcinoma (3 by 2.5 by 2 cm.) with involvement of serosa	+	Mucosa	IV	4	10 mm.
16	Carcinoma (6 by 5 by 2 cm.); involvement of lymphatic serosa	—	Submucosa	IV	4	5 mm.
17	15 cm. stomach; carcinoma (10 by 7 by 2 cm.) with extensive involvement of nodes	+	Submucosa	III	4	8 mm.
18	13 cm. stomach; adenocarcinoma (8 by 8 by 3 cm.)	+	Serosa	III	3	5 mm.
19	20 cm. adenocarcinoma (8 by 6 by 2 cm.)	+	Submucosa	II	2	No extension
20	15 cm. stomach, 11 cm. of which is small cell, diffuse carcinoma (linitis plastica type) with involvement of serosa	+	All coats	IV	4	Not clear; at least 35 to 40 mm.
21	6 cm. stomach; diffuse carcinoma (linitis plastica type)	..	Mucosa	IV	3	Not clear; no edge
22	13 cm. stomach; carcinomatous ulcer (4 cm. diameter by 5 mm. deep)	—	Submucosa	III	3	10 mm.
23	15 cm. stomach; carcinoma (3 cm. diameter by 12 mm. deep) with involvement of serosa	+	Serosa	III	3	At least 22 mm.; not clear
24	Polypoid solid adenocarcinoma (10.5 cm. diameter) projecting into lumen	+	Submucosa	II	3	12 mm.
25	14 cm. stomach; colloid carcinoma (10 by 6 cm.)	+	Submucosa	III	3	11 mm.
26	15 cm. stomach; adenocarcinoma (5.5 by 5 by 2 cm.)	+	Mucosa	III	3	7 mm.
27	12 cm. stomach; ulcerating fibrosarcoma (5 by 5 by 2 cm.)	—	Submucosa	..	3	5 mm.
28	13 cm. stomach; diffuse carcinoma	—	Serosa	IV	4	No edge
29	8 cm. stomach; carcinomatous ulcer (6 cm. diameter) with involvement of pylorus	..	Mucosa	III	3	10 mm.
30	12 cm. stomach; diffuse carcinoma	—	Mucosa	IV	3	Not clear; no edge
31	Diffuse carcinoma (4 cm. diameter) with small area of ulceration (1 cm. diameter; linitis plastica type)	+	Submucosa	IV	4	30 mm.

TABLE 1.—*Summary of Material—Continued*

Case	Description of the Pathologic Condition	Involvement of Lymph Nodes	Plane of Maximal Extension	Classification by Extension	Broders' Grading	Distance of Lateral Extension
32	13 cm. stomach; carcinoma (4 by 4 by 1.5 cm.) at pylorus; very few nodes attached	—	Mucosa	IV	4	8 mm.
33	12 cm. stomach; papillary adenocarcinoma (9 by 7 by 1.5 cm.)	—	Mucosa	II	2	No extension
34	12 cm. stomach; papillary carcinoma (7 by 6 by 2 cm.)	+	Submucosa	II	2	No extension
35	Ulcerated carcinoma (4 by 4 by 1.5 cm.); very few nodes attached	—	Submucosa	III	4	10 mm.
36	Stomach; carcinoma (5.5 by 4 by 1 cm.)	—	Submucosa	III	3	No extension
37	Portion of stomach; polypoid adenocarcinoma (6 by 5 by 3 cm.) projecting into lumen	—	Mucosa	II	2	No extension
38	15 cm. stomach; diffuse small cell carcinoma with very early colloid changes	—	Submucosa	IV	4	No edge
39	12 cm. stomach; adenocarcinoma (4 by 4 by 1 cm.)	..	Serosa	II	3	No extension
40	12 cm. stomach; shallow carcinomatous ulcer (5 cm. diameter); no nodes attached	..	Submucosa	IV	4	Not clear; at least 20 mm.
41	Carcinomatous polyp (9 by 6 by 6 cm.)	+	Mucosa	II	2	No extension; multicentric
42	Carcinomatous ulcer (6 cm. diameter; linitis plastica type)	—	Submucosa	IV	4	No edge
43	12 cm. stomach; carcinomatous ulcer (4 by 4 by 1.5 cm.)	+	Submucosa	IV	4	No extension
44	9 cm. stomach; carcinomatous ulcer (6 by 5 by 1 cm.)	+	Serosa	II	3	No extension
45	9 cm. stomach; adenocarcinoma (7 by 9 by 2 cm.)	+	Submucosa	II	2	No extension
46	13 cm. stomach; ulcerated and perforated adenocarcinoma (8 by 9 by 2 cm.)	+	Submucosa	II	2	No extension
47	14 cm. stomach; ulcerated carcinoma (4 by 4 by 1 cm.)	+	Serosa	IV	4	Not clear; at least 35 mm.
48	12 cm. stomach; carcinomatous ulcer	+	Serosa	IV	4	25 mm.
49	9 cm. stomach; adenocarcinoma (3 by 3 by 1 cm.) just above pylorus; in places producing colloid	+	Serosa	IV	4	No edge; 5 mm.
50	12 cm. stomach; ulcerated carcinoma (6 by 5 by 2 cm.) with involvement of serosa	—	Submucosa	II	2	No extension

quently is most likely to pass through hidden, lateral extensions in the apparently healthy gastric wall. Second, the lesser curvature is more abundantly supplied with lymphatic structures than any other part of the stomach, and, as it is known that carcinoma habitually extends by the lymphatic system, the farthest extensions of the growth would naturally be expected to be on the lesser curvature.

Occasionally it was found that the tumor did not reach the lesser curvature; in these cases the block was cut parallel to the lesser curvature and as near it as possible. Care was taken to include part of the tumor in the block, as well as all the apparently healthy tissue between the tumor and the resected edge of the stomach. In some cases the edge of the tumor was indistinct, and in these I used my judgment with regard to the edge. In other cases it was impossible to identify any edge of the tumor; these tumors were noted as having "no edge."

Cutting of Frozen and Paraffin Sections from Block.—The frozen and paraffin sections were stained in the usual manner with hematoxylin and eosin. Both groups of slides were subjected to microscopic examination.

Microscopic Examination of Slides.—The macroscopic edge of the tumor was first marked on the slide, that is, the "raised edge," indicated in figure 1. The carcinoma was then followed out to the point of maximal extension from the edge. This point was also marked on the slide, and the distance between the two points was measured in millimeters. At the same time, the plane of maximal extension in the gastric wall was noted.

Classification of Tumor According to Anatomic Manner of Extension from Edge of Growth.—The tumors were originally placed in three classes, I, II and III. Broders, in grading these tumors, did not find any which could be graded I; consequently, to avoid confusion, the original three classes were raised to II, III, and IV, so as to coincide with Broders'[11] grading. In class II, then, there was little if any lateral extension; in class III, moderate lateral extension, and in class IV, much lateral extension.

Study of Differentiation, Lymphocytosis and Fibrosis (MacCarty[12]).—These factors have been shown to bear a definite relation to the period of survival following removal of carcinoma. Lymphocytosis and fibrosis are part of nature's defensive mechanisms against the advance of carcinoma. Lymphocytosis was frequently noted, and in its presence the advance of the carcinoma appeared to be retarded. Fibrosis was not observed, except to a slight extent.

Grading According to Broders.—Broders himself graded each of these tumors after my classification was already recorded. It will be shown that classification and grading gave similar results.

RESULTS

With regard to the plane of extension, gastric carcinomas can be placed in three other groups according to whether they extend farthest in the mucosa, submucosa or serosa. Figure 1 indicates the manner in which carcinoma extends into the gastric wall.

The majority of carcinomas spread in the manner of the uppermost diagram in figure 1. It is seen that the tumor extends outward in the submucosa to a point well removed from the apparent limit of the disease. This extension in the submucosa takes place subjacent to healthy mucosa; there is nothing to indicate that the underlying tissues are affected. It might be supposed that the edge of the ulcer marked the limit of the disease; however, only microscopic examination can reveal the true state. The carcinoma extends first from the mucosa, through the muscularis mucosa, into the submucosa. Here its rapid extension is favored both by the rich supply of lymphatic channels and by the

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11. Broders, A. C.: Squamous-Cell Epithelioma of the Lip. A Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. **74:**656 (March 6) 1920.

12. MacCarty, W. C.: Factors Which Influence Longevity in Cancer. A Study of 293 Cases, Ann. Surg. **76:**9 (July) 1922. MacCarty, W. C., and Kehrer. J. K. W.: Possible Defensive Factors in Cancer of the Rectum. A Study of 102 Cases, J. Lab. & Clin. Med. **7:**602 (July) 1922. Sistrunk, W. E., and MacCarty, W. C.: Life Expectancy Following Radical Amputation for Carcinoma of the Breast. A Clinical and Pathologic Study of 218 Cases, Ann. Surg. **75:**61 (Jan.) 1922. MacCarty and Mahle.[5]

loose areolar tissue which offers little resistance to the advancing cells [13] (figs. 2 and 3).

The muscular coats of the stomach offer great resistance to the advancing carcinoma, and the cells of the tumor are usually found going through the muscular coats by way of the intermuscular lymphatic structures, to reach the serosa, where another rich· network of lymphatic channels favors their rapid extension.
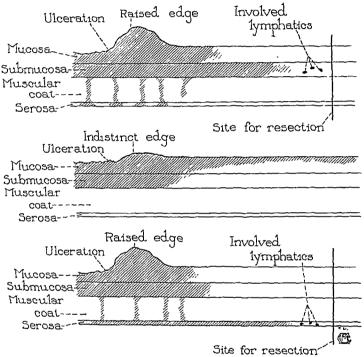

Fig. 1.—The manner of extension of carcinoma in the gastric wall.

The favorite plane for lateral extension in the gastric wall is the submucosa. Of fifty cases, maximal extension was in the submucosa in twenty-nine, in the mucosa in eleven, in the serosa in eight, in both the submucosa and serosa in one and in all coats in one. Extension in the mucous and serous coats remains to be considered.

It has been noted that the main extension was in the mucosa in eleven cases. This extension manifests itself in three ways. The first is the obvious and familiar polypoid carcinoma; these tumors have no deceptive underground ramifications. They have long been regarded as relatively harmless. W. W. Mayo [14] used to remark that the carcinoma

13. Jamieson, J. K., and Dobson, J. F.: The Lymphatic System of the Stomach, Lancet **1**:1061 (April 20) 1907.

14. Mayo, W. W., quoted by Broders.[11]

Fig. 2 (case 4).—Typical mode of extension in the submucosa; carcinoma 8 mm. from the edge of the ulcer.

Fig. 3 (case 13).—Outlying malignant cell nest in the submucosa 11 mm. from the edge of the ulcer; × 125.

that grows toward one is not as dangerous as that which grows away from one.

The second type of carcinoma which has its main extension in the mucosa is diagrammatically represented in the middle section of figure 1. This type was present only twice (cases 21 and 30). Here the carcinoma was found spreading on the surface of the mucosa, over and between normal gastric glands. The impression I received was that this type of carcinoma spreads over the surface so rapidly that it does not have time to attack the deeper parts of the mucosa. In the two cases mentioned, the carcinoma extended down to the submucosa in the older part of the tumor. There was no visible edge (figs. 4, *A* and *B*). This is a very deceptive type from the surgeon's point of view, for the tumor has no visible edge, nor is there any thickening of the gastric wall which might help him to define the limits of the disease. Fortunately, this condition is comparatively rare.

In the third type in which extension is in the mucosa the extension may reach its maximal distance from the visible edge of the growth by involving the whole thickness of the mucosa without penetrating the submucosa. Case 32 illustrates this point; the submucosa had been penetrated at the older part of the tumor, but the extension, while involving the whole thickness of the mucosa, did not penetrate the muscularis mucosa (figs. 5, *A* and *B*).

Finally, the maximal plane of lateral extension may be in the serosa; this occurred, as has been noted, eight times in this series of fifty cases. When carcinoma involves the serosa, for some reason or other it fails to extend very far in the submucosa, but traverses the intermuscular lymphatic channels to reach the serosa, where its maximal extension takes place (fig. 6). The lowermost diagram in figure 1 illustrates this type of extension in the serosa, where rapid extension is favored by the abundance of lymphatic channels. It is interesting to note that in this series of fifty gastric carcinomas, in six cases lateral extension was more than 20 mm. from the edge of the growth, and in five of these the serosa was the plane of maximal lateral extension. In one of these five cases all coats were equally involved and in another the submucosa and serosa were involved to the same extent. In this series there was not a case of involvement of the serosa without metastasis to lymph nodes.

From the foregoing statements it will be obvious that in many cases the raised, palpable edge of a gastric carcinoma does not indicate the line of demarcation between diseased and healthy tissue; therefore, I was led to try to find some means of estimating the extent to which a given carcinoma will be likely to invade the surrounding gastric wall. It was found that an estimate could be made in two ways: A study of the differentiation of the tumor according to MacCarty will give a rough

Fig. 4 (case 30).—*A*, diffuse spread of carcinoma over surface of stomach. *B*, higher magnification of part of *A*. The large "one-eyed" cell can be identified in both photomicrographs.
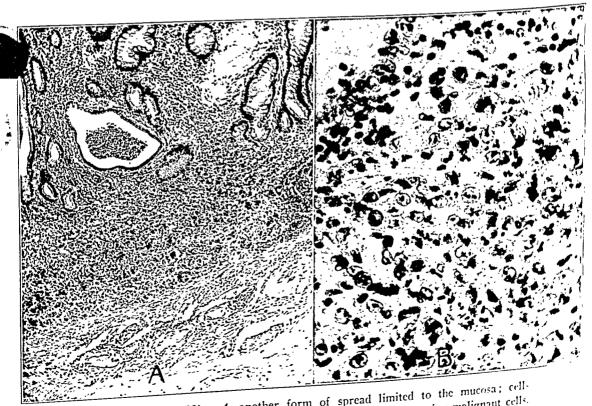

Fig. 5 (case 32).—*A*, another form of spread limited to the mucosa; cell 8 mm. from edge of ulcer. *B*, higher magnification of *A* showing malignant cells.

indication, as will the system of grading according to Broders. I shall correlate the grading of the tumors by Broders' method with the classification by the amount of lateral extension. It will be shown that the greater degree of lateral extension is to be expected among carcinomas of higher grade. The same principle is true of the differentiation of tumors according to MacCarty; the less the differentiation of the cells, the more likely is the tumor to have wide lateral extension. The grad-
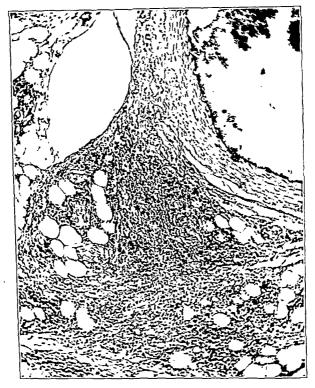

Fig. 6 (case 48).—Malignant cells in the serosa, 25 mm. from the edge of the ulcer.

ing, differentiation, and amount of lateral extension appeared in many cases to be parallel. For the guidance of those who wish to compare the two methods, differentiation and grading, it can be said that tumors of grade 2 are fairly well differentiated, those of grade 3, poorly differentiated, and those of grade 4, undifferentiated.

The fifty carcinomas were studied to determine the lateral extension in millimeters according to their grading by Broders' method. In eleven cases (cases 1, 6, 9, 19, 33, 34, 37, 41, 45, 46 and 50) in which the carcinomas were of grade 2, there was apparently no lateral extension. In table 2 it can be seen that carcinomas of grade 3 extend widely and that those of grade 4 extend most widely.

A little explanation is needed for those extensions and their measurements. Any carcinoma that extended less than 5 mm. was regarded as not having any lateral extension. In some cases the surgeon was unable to resect clear of the growth, and these cases are indicated by the words "not clear." In most cases the edge of the tumor was distinct, and the limit of malignant extension into healthy tissue could be distinguished. However, these measurements are not absolutely accurate, for it is impossible to measure a series of carcinomas to a millimeter. Nevertheless, it should be remembered that the personal error is common to all the specimens, and the figures are sufficiently accurate to bring out some interesting points.

TABLE 2.—*Amount of Lateral Extension of Gastric Carcinomas*

20 Carcinomas, Graded 3		19 Carcinomas, Graded 4	
Case	Lateral Extension in Millimeters	Case	Lateral Extension in Millimeters
2	10	3	30 (not clear)
4	8	7	No extension
5	No edge	8	5 (not clear)
10	No extension	14	5 (not clear)
11	10	15	10
12	6	16	5
13	11	17	8
18	5	20	40 (not clear)
21	No edge (not clear)	28	No edge
22	10	31	30
23	22 (not clear)	32	8
24	12	35	10
25	11	38	No edge
26	7	40	20 (not clear)
27	5	42	No edge
29	10	43	No extension
30	No edge (not clear)	47	35 (not clear)
36	No extension	48	25
39	No extension	49	No edge
44	No extension		

Among the carcinomas graded 3 (table 2), in three instances the surgeon did not resect clear of the growth; in two of these cases the tumor had no visible edge. It is interesting to note that both these tumors were of the unusual type which extends solely over the surface of the mucous membrane. At the oldest part of the neoplasm there was some extension downward into the submucous and muscular coats, but all of the lateral extension was over the surface of mucous membrane of the stomach; the carcinomatous material looked as if applied like a coat of paint. These tumors were both classified by MacCarty as undifferentiated tumors and highly malignant. In such circumstances the surgeon has no means of estimating at what point his resection should be carried out, and extends it as high on the lesser curvature as possible. In the third case in which the surgeon failed to resect clear of the growth it had extended 22 mm. from the edge of the ulcer. This was case 23, and it will be noted that the maximal extension was in the

serosa. On consulting the history of this case it was found that the patient had had symptoms for two years, or thirteen months longer than the average history given in cases of gastric carcinoma in the clinic (McVicar[15]). It is conceivable that if a carcinoma is left long enough, especially if there is involvement of the serosa, there is practically no limit to the possible distance of the extension. It may be stated that as a rule carcinomas graded 3 may extend a distance of 15 mm. from the visible edge of the ulcer. The average lateral extension in the sixteen carcinomas graded 3 measured 6.56 mm.

On six occasions the line of resection was through the growth in spite of the fact that on four occasions the gastrectomy was done at least 20 mm. from its edge. Cases 7 and 43 (table 2), in which there was no lateral extension, require a little explanation. The tumors in both of these cases were very active, and belonged to the class of "small cell" carcinoma; in fact, they resembled lymphosarcoma, and there was discussion before it was decided to call the tumor in case 7 small cell carcinoma and not lymphosarcoma. Another point of similarity in these two tumors was the very active lymphocytic barrier thrown out by the tissues against the advancing malignant cells. I would suggest that these were two very active and rapidly advancing tumors which did not have sufficient time to send out the usual offshoots. The growth was so rapid that the edge of the tumor kept moving centrifugally. It will be observed that on one occasion the resection was carried out about 40 mm. away from the edge of the tumor, yet the surgeon was unable to remove all of it. The average extension of nine carcinomas graded 4 was 10.66 mm.

Only sixteen of twenty carcinomas graded 3 and only nine of nineteen graded 4 could be measured from the edge of the ulcer to the limit of lateral extension; that is, in some there was not a definite edge from which to measure, and in others the resection was done through tumor cells. However, if tumors of both grades in which there was "no edge" are excluded, but if those which bear the notation "not clear" are included, measuring these up to the line of resection, more reliable material is obtained from which to make deductions. By this plan, the average lateral extension in seventeen carcinomas graded 3 was 7.47 mm. and in fifteen carcinomas graded 4 it was 15.4 mm. Broadly speaking, the carcinomas of various grades extend as would be expected; extension of those of grade 3 is about halfway between the extensions of those of grades 2 and 4. Apparently, this classification is also borne out by the difficulties of the surgeon. Of eleven cases of carcinoma graded 2, there was no lateral extension in any, and all were resected clear of

15. McVicar, C. S., and Daly, Joseph: The Diagnosis of Operable Carcinoma of the Stomach, Ann. Int. Med. **1**:145 (Sept.) 1927.

the growth. Of twenty cases in which the carcinoma was graded 3 there was no lateral extension in four cases; lateral extension was between 5 and 22 mm. in twelve cases, and resection was not clear of the

TABLE 3.—*Distance and Plane of Extension in Cases in Which There Was No Involvement of Lymph Nodes*

Case	Grade	Distance in Millimeters	Plane of Maximal Extension
1	2	10	Submucosa
2	4	10	Submucosa
7	4	No extension	Submucosa
12	3	6	Submucosa
16	4	5	Submucosa
22	3	10	Submucosa
27	3	5	Submucosa
30	3	No edge (not clear)	Mucosa
32	4	8	Mucosa
33	2	No extension	Mucosa
35	4	No extension	Submucosa
36	3	No extension	Submucosa
37	2	No extension	Mucosa
38	4	No edge	Submucosa
42	4	No edge	Submucosa
50	2	No extension	Submucosa

TABLE 4.—*Distance and Plane of Extension in Cases in Which There Was Involvement of Lymph Nodes* *

Case	Grade	Distance in Millimeters	Plane of Maximal Extension
3	4	30	Submucosa, serosa
4	3	8	Submucosa
5	3	No edge	Submucosa
6	3	No extension	Submucosa
8	4	Not clear	Submucosa
9	2	No extension	Submucosa
10	3	No extension	Submucosa
11	2	No extension	Mucosa
13	3	11	Submucosa
14	4	Not clear	Mucosa
15	4	10	Mucosa
17	4	8	Submucosa
18	3	5	Serosa
19	2	No extension	Submucosa
20	4	Not clear	All coats
23	3	Not clear	Serosa
24	3	12	Submucosa
25	3	11	Submucosa
26	3	7	Mucosa
31	4	30	Submucosa
34	2	No extension	Submucosa
41	2	No extension	Mucosa
43	4	No extension	Submucosa
44	3	No extension	Serosa
45	2	No extension	Submucosa
46	2	No extension	Submucosa
47	4	Not clear	Serosa
48	4	25	Serosa
49	4	No edge	Serosa

* Five cases with involvement of nodes not included.

growth in three cases. Of nineteen cases of carcinoma graded 4, there was no lateral extension in two cases; lateral extension was between 5 and 40 mm. (in five, more than 22 mm.) in thirteen cases, and resection was not clear of the growth in six cases.

In tables 3 and 4 is given the amount of lateral extension of carcinomas of the stomach without and with nodal involvement, respectively.

It will be seen that the carcinomas of the stomach with nodal involvement extended more widely than those without involvement, and that most of the resections which did not include the whole of the tumor were performed in those cases in which there was nodal involvement.

SUMMARY AND CONCLUSIONS

In gastric carcinomas the raised, rampart edge of the ulcer may not mark the limit of invasion of the gastric wall. The amount of extension from the edge of a gastric carcinoma varies according to the degree of differentiation (MacCarty) and the grading (Broders). In the most diffuse carcinomas of the stomach, the growth has no visible edge, and a proper point for resection cannot be indicated; in all other types of gastric carcinoma a distance of at least 4 cm. of healthy gastric wall should be allowed from the edge of the ulcer along the lesser curvature toward the cardia, in order that the resection may include the whole of the primary focus. This small series tends to indicate that whenever the serosa is involved, nodal metastasis will be present.

CHRONIC PANCREATITIS ASSOCIATED WITH PEPTIC ULCER

J. WILLIAM HINTON, M.D.

Associate Professor of Surgery, New York Post-Graduate Medical School,
Columbia University; Associate Visiting Surgeon, Bellevue Hospital

NEW YORK

The conservative treatment of peptic ulcer is generally admitted by internists and surgeons to be the proper procedure to follow as long as symptomatic relief can be obtained. The difficulty comes in determining when the patient will not respond further to medical care and must be operated on. It is my experience [1] that one need not fear that a gastric ulcer will become malignant; at least, this should not be used as an argument for referring patients for operation, since the mortality due to gastric resection in the hands of experienced surgeons exceeds the incidence of malignant transformation. In the clinic with which I have been associated, patients with gastric ulcer have received conservative treatment for the past five years without malignant degeneration.

There is one true indication for operation, and that is uncontrollable pain, which is rarely due to an uncomplicated ulcer but results when an adjacent viscus becomes adherent to the ulcerated area. In the majority of instances the organ involved is the pancreas, which becomes chronically infected; at least, the enlargement and induration of the pancreas must be clinically attributed to chronic infection. There is a great deal of discussion as to the etiology of chronic interstitial pancreatitis, but in this presentation I shall not enter into the theories of the disease, which have been discussed in a previous presentation.[2] I shall consider only the clinical significance of pancreatic lesions in relation to peptic ulcer.

In the gastro-enterologic clinic of the Fourth Medical and Surgical Divisions of Bellevue Hospital, which ended its fifth year in December, 1932, my associates and I had occasion to observe 583 patients suffering from peptic ulcer. Of this group there were 440 who were not operated on and 143 who had been operated on before entering the clinic. Of the patients operated on, 71 were operated on for chronic ulcer and 72 for

1. Hinton, J. W.: The Clinical Consideration of Gastric Ulcer and Carcinoma, Arch. Surg. 27:395 (Aug.) 1933.

2. Hinton, J. W.: Chronic Interlobular Pancreatitis, Ann. Surg. 96:441 (Sept.) 1932.

acute perforated ulcer. It was the purpose of the clinic to determine the best method or the best combination of methods to be used in treating these patients conservatively; therefore we referred patients for operation only as a last resort. The one indication which was accepted as a true indication for surgical intervention was pain which no method of medical treatment would relieve. During this period of five years we referred only 33 patients from the clinic for operation. In some of these cases the associated pancreatitis was so striking that the cases seem worthy of reporting.

REPORT OF CASES

CASE 1.—A man, aged 52, was admitted to the Fourth Surgical Division, Bellevue Hospital, on Jan. 26, 1928. He had been operated on in another hospital on Dec. 15, 1927.

He was jaundiced, and complained of abdominal pain. He was receiving $\frac{1}{6}$ grain (0.01 Gm.) of morphine three times a day. A résumé of the operative findings from the other institution was: carcinoma of the head of the pancreas with metastasis to the spine. In view of this diagnosis, it was thought advisable to make a roentgenologic examination of the intestinal tract, in order to demonstrate the pancreatic tumor. Roentgenologic study revealed, however, that the patient had a duodenal ulcer. A Sippy diet was instituted. Within one week the patient had so improved that he was no longer given morphine. He was discharged from the hospital on Feb. 12, 1928, and was followed in the gastro-enterologic clinic until April 23. On this date he was readmitted to the hospital because of severe pain which he had had for two weeks; previous to this, however, he had been symptomatically well for two months. Dr. John H. Morris operated on the patient on April 26. An ulcer was found in the duodenum with an induration of the head of the pancreas the size of a large lemon. A gastro-enterostomy was performed; the gallbladder and appendix were found to be normal and were not removed. After the operation, the patient was followed regularly in the clinic; he had no jaundice but had frequent complaints referable to the bladder. The results of urologic examinations were of no significance. The patient was last seen on Jan. 26, 1933.

CASE 2.—A man, aged 52, was admitted to the gastro-enterologic clinic of the Fourth Medical and Surgical Divisions at Bellevue Hospital on Jan. 12, 1929, with a roentgenologic diagnosis of pyloric ulcer. The patient was given a Sippy diet and was symptomatically well until September 28. Roentgenograms on June 14 and on October 3 revealed no abnormalities. When the symptoms recurred the pain could not be relieved by conservative treatment, although a series of roentgenograms of the gastro-intestinal tract showed nothing abnormal. The patient was advised to enter the hospital. I operated on him on November 9. When the abdomen was opened, the gallbladder was found to be normal; the duodenum was mobile and easily inspected; there was no evidence of ulcer on the anterior surface, but a slightly indurated area was felt posteriorly, and the head of the pancreas was the size of a lemon. A posterior gastro-enterostomy and an appendectomy were performed, from which the patient made an uneventful recovery. He was followed regularly in the clinic; he remained symptomatically well and roentgenologically normal. He was last seen on Jan. 19, 1933.

CASE 3.—A man, aged 59, was admitted to the hospital on Aug. 21, 1930, complaining of epigastric pain after meals, with periodicity for twenty years; during the two years prior to admission he had had persistent pain which was more severe at night. Roentgenologic examination on August 15 revealed a duodenal ulcer without obstruction. A Sippy diet was tried for two weeks, without affording the patient relief. Operation on September 5 revealed the gallbladder to be olive green and not thickened, but there was a duodenal ulcer with the duodenum fixed to the pancreas, and the head of the latter organ felt the size of a lemon. A posterior gastro-enterostomy without clamps and a routine appendectomy were performed. Convalescence was uneventful; the patient improved, but still experienced some discomfort. He was last seen on Jan. 5, 1933.

CASE 4.—A man, aged 32, was admitted to the clinic on Dec. 1, 1928, complaining of abdominal pain after meals. He had had these attacks for seven years and for the last year the pain had been severe; food gave little relief. Roentgenologic study on Nov. 25, 1928, had revealed a duodenal ulcer without obstruction. The patient was given an ambulatory Sippy diet, wtihout relief, and then was given streptococcus vaccine. After four and a half months of conservative treatment his condition had not improved; he was having pain at night constantly. Operation on April 25, 1929, disclosed a duodenal ulcer, with the pancreas enlarged and the duodenum adherent to the gland. A posterior gastro-enterostomy without clamps and a routine appendectomy were performed. The gallbladder was thickened and chronically diseased, but it was not removed, owing to the fact that the patient had shown poor anesthesia. An uneventful convalescence followed. The patient was observed regularly after leaving the hospital; he remained symptomatically improved, but was not entirely well. He was last seen on Dec. 29, 1932.

CASE 5.—A woman, aged 36, was admitted to the clinic on March 17, 1928, complaining of periodic pain after meals. She had entered Bellevue Hospital on June 15, 1925, because of pain in the right upper quadrant of the abdomen which was cramplike and which radiated to the right shoulder. At that time she also complained of pain after meals, which, however, was relieved by food. A diagnosis of cholecystitis and cholelithiasis was made, and the patient was operated on on June 20. A chronic cholecystitis was found but no stones. Also a duodenal ulcer was found which was pronounced healed. A cholecystectomy was performed, but the stomach was not operated on. The patient was readmitted on Dec. 21, 1925, complaining of pain in the upper part of the abdomen which had been present for three months. The pain was similar to that for which she had been operated on before. Roentgenologic examination revealed a duodenal ulcer, and the patient was given a Sippy diet. She remained in the hospital until Jan. 12, 1926, and was discharged symptom-free, but was readmitted on May 26 because of pain. Roentgenologic study revealed a duodenal ulcer. The patient was operated on on June 3, but the operating surgeon, who also performed the first operation, did not find an ulcer; so the abdomen was closed. The patient returned to the follow-up clinic at irregular intervals for the next year and a half but was constantly complaining of pain.

On entering our clinic, March 17, 1928, the patient stated that she had not been relieved by either operation, and that she was much worse than before. Her chief complaint was pain after meals, which was usually relieved by food; the pain was becoming so severe that it kept her awake at night. Roentgenologic study revealed a duodenal ulcer. The patient was given medical treatment, but she was uncooperative, returning only at irregular intervals. A year later she

was advised to permit herself to be operated on, as her condition was growing worse, but she refused. She returned to the clinic at irregular intervals until Sept. 5, 1930, when the pain became so severe that she entered the hospital of her own accord. She was operated on on September 12. The duodenum was found to be adherent to the pancreas, and the head of the latter was enlarged to the size of a large lemon. A posterior gastro-enterostomy was done. The patient was greatly improved. When last seen on Feb. 2, 1933, she complained of gas after meals, but had no pain.

CASE 6.—A man, aged 30, was admitted to the clinic on July 7, 1929, complaining of pain in the upper part of the abdomen. The history was unimportant. The patient had had epigastric discomfort for ten years. Eating gave relief from the symptoms, which were probably never very severe, as the patient first sought medical treatment two weeks before admission. At that time a roentgenogram revealed a duodenal ulcer. The patient was given an ambulatory Sippy diet and did well for four months; then his symptoms returned, and he was given vaccines, without improvement. The patient gained 20 pounds (9 Kg.) while under treatment; he was heavier than ever before, his weight being 180 pounds (81.6 Kg.). The medical treatment was continued until May 20, 1930, when he was advised to enter the hospital for operation, although he had maintained his weight. Operation on May 24 revealed a duodenal ulcer and an adhesion of the duodenum to the pancreas, with the head of this organ enlarged and firm. A posterior gastro-enterostomy was performed, and the patient was symptom-free thereafter. He was last seen on Sept. 28, 1932.

CASE 7.—A man, aged 57, was admitted to the hospital on Oct. 9, 1930, complaining of severe abdominal pain; he said that he had been treated for an ulcer. For twenty years the patient had had pain after meals, and for fifteen years he had known that he had an ulcer, for he had been treated for it by different physicians. Eight weeks before coming under our observation, he was under the care of a prominent gastro-enterologist and was treated with a duodenal tube for four weeks. The pain was so severe that he was unable to sleep, and owing to the severe pain he was referred to the hospital with a diagnosis of complicating cholecystitis and cholelithiasis, though the dye test was negative. After admission the patient required codeine for the pain; he refused to have further roentgenograms of the gastro-intestinal tract made; an exploratory laparotomy was therefore performed on October 15, which revealed a normal gallbladder, a duodenal ulcer and an enlargement of the pancreas to the size of an orange. A posterior gastro-enterostomy and a routine appendectomy were performed; following the operation the patient was fairly free from symptoms. However, he had two exacerbations of symptoms. He was last seen on Dec. 29, 1932.

CASE 8.—A man, aged 30, was admitted to the clinic on April 28, 1931, stating that he had been treated in the medical wards for an ulcer. A résumé of the hospital records revealed that he had entered the wards on April 3, and that he had been discharged on April 25. He gave a history of epigastric distress of six years' duration, which was getting more severe. Roentgenologic examination revealed a duodenal ulcer without retention at the end of six hours. The patient was treated by a Sippy diet while in the hospital, and was discharged improved. He did not continue to receive treatment at the clinic, but on October 4, having severe pain, he entered the emergency ward; there he was advised to go to the hospital as a ruptured ulcer was suspected. On examination, the diagnosis of duodenal ulcer and chronic pancreatitis was made, and an operation was advised. The operative findings on October 9 were chronic cholecystitis, duodenal ulcer and

chronic pancreatitis, as the head of the gland was the size of a lemon. A cholecystectomy, appendectomy and posterior gastro-enterostomy were performed. The patient improved after the operation. He was last seen Nov. 17, 1932.

CASE 9.—A man, aged 38, was admitted to the hospital on July 17, 1931, complaining of abdominal pain after meals. The history was not important except for the illness in question. The patient had had pain in the upper abdominal region for ten years and during the two years prior to admission it had been much more severe. He was treated in the medical wards from June 10 to June 29 and given a Sippy diet. Roentgenologic study revealed a duodenal ulcer without retention at the end of six hours. A vitamin diet with yeast was instituted without relief; the diet was then changed to an ambulatory Sippy diet with Saunders' streptococcus vaccine intravenously, without relief. On August 29, owing to the severe pain and a diagnosis of duodenal ulcer and pancreatitis, the patient was advised to enter the hospital. Operation on September 3 revealed a duodenal ulcer and an enlarged pancreas, with the duodenum adherent to it. The gallbladder was normal. A posterior gastro-enterostomy and a routine appendectomy were performed, but the patient continued to have pain. After persistent medical care, without relief of pain, a subtotal resection was performed on Oct. 10, 1932. The patient died of pneumonia six days afterward.

CASE 10.—A man, aged 25, was admitted to the hospital on Dec. 30, 1929, complaining of abdominal pain after meals. The history except for the illness revealed nothing of consequence. The patient stated that he was seized with severe pain on July 5, and that he was operated on for a ruptured ulcer in the Jersey City Hospital. A report from that hospital was to the effect that the operation had revealed a ruptured duodenal ulcer, and that a simple closure had been performed. The patient said that he had had abdominal discomfort after meals for two years before the perforation occurred, and that following the operation he was well for two months, but that for the past four months he had had abdominal pain after meals, which was getting worse. Roentgenologic study on Jan. 3, 1930, revealed a duodenal ulcer without retention at the end of six hours. He was treated in the wards for one week and then referred to the clinic, which he entered on January 11. An ambulatory Sippy diet, Saunders' vaccine, administered intramuscularly, and nonspecific protein therapy with a milk preparation failed to give permanent relief, and the patient was admitted to the hospital on October 20 for operation, with the diagnosis of duodenal ulcer and chronic pancreatitis. Operation on October 25 revealed a duodenal ulcer and enlargement of the pancreas to the size of a large lemon, with the duodenum adherent to it. The gallbladder was normal. A posterior gastro-enterostomy and appendectomy were performed. The patient remained clinically well. He was last seen on Jan. 12, 1933.

CASE 11.—A man, aged 39, was admitted to the clinic on July 10, 1930, complaining of abdominal pain after meals and severe pain at night. The history except for the illness was not significant. Since 1914 the patient had had abdominal pain after meals, and in 1916 the condition was diagnosed as ulcer. In 1917 the patient was operated on in Dublin, Ireland. The ulcer was found, but it was pronounced healed; the appendix was removed. The patient obtained no relief from the operation; his condition became gradually worse, and at night he was kept awake from one to two hours with pain. Roentgenologic study revealed a duodenal ulcer with retention at the end of six hours. The patient was treated with an ambulatory Sippy diet and was given Saunders' vaccine intramuscularly, with only slight relief. He refused to enter the hospital for rest in bed, as he had

been treated in two other hospitals during the past year by a Sippy diet with only slight improvement. After five months of treatment, operation was advised; the diagnosis was duodenal ulcer and chronic pancreatitis. On Dec. 12, 1930, the operation was performed; it disclosed chronic cholecystitis, a duodenal ulcer and an enlarged, firm pancreas adherent to the duodenum. A posterior gastro-enterostomy and cholecystectomy were performed. Following the operation, the patient was well for one year, but at that time had a moderate hemorrhage. He has not been seen since.

CASE 12.—A man, aged 25, was admitted to the hospital on Sept. 4, 1931, complaining of severe abdominal pain that had lasted for two hours. The history revealed that on Dec. 29, 1929, he was operated on for perforated ulcer without suturation of the ulcer. Dr. Fischel, his family physician, stated that when the abdomen was opened, gas and free fluid escaped, but that the perforation was not found and cigaret drains were inserted. The patient made an uneventful recovery and was symptom-free until Sept. 4, 1931. Two hours before admission to the hospital he was seized with sudden abdominal pain, and Dr. Fischel again diagnosed the condition as perforated ulcer. The operation was performed by Dr. Briedenbach. On opening the abdomen, he found gas and free fluid, but he could not find the perforation, as the duodenum was adherent to the pancreas and the latter organ was enlarged. Drains were inserted, and an uneventful convalescence followed. The patient entered the clinic on September 24, and was followed regularly until October 23, when he had another attack of severe abdominal pain which necessitated admission to the hospital. During the observation in the clinic he was purposely not studied roentgenologically, as we feared that a perforation might result from the manipulation, but at about 4 a. m. on October 23, he was seized with sudden pain, and a boardlike rigidity set in. The operation was again performed by Dr. Briedenbach. When the peritoneum was opened, no gas or free fluid was encountered. The duodenum was adherent to the pancreas, and the latter was hard and twice its normal size. The capsule was perforated, and drains were inserted. Convalescence was uneventful. The patient was not followed after his departure from the hospital, as he left the city.

CASE 13.—A woman, aged 47, was admitted on Feb. 14, 1930, complaining of severe colicky pain in the upper part of the abdomen of three weeks' duration. She had a hysterectomy in 1921 and an operation for disease of the gallbladder in 1923, but did not know whether or not the gallbladder had been removed. Since the operation for disease of the gallbladder she had had other attacks of rather severe pain in the upper abdominal regions, but none so severe as the cramplike pains which she had had in the last three weeks. Roentgenologic examination on Feb. 24, 1930, by the dye method did not reveal the gallbladder, and the series of roentgenograms of the gastro-intestinal tract revealed that the duodenal bulb was diminished, but showed no definite ulcer, although there was a retention of two thirds of the meal at the end of six hours. The preoperative diagnosis was cholecystitis and cholelithiasis. The patient was operated on on February 26 by Dr. Morris. An induration was found in the descending portion of the duodenum which was interpreted as an ulcer perforating into the pancreas. A posterior gastro-enterostomy was performed. Three days postoperatively pain and tenderness developed in the right lower quadrant which it was suspected were due to leakage from the ulcer. The area was opened, and the duodenal contents were obtained. The patient had a stormy convalescence, with three intra-abdominal abscesses, which were drained. She was discharged on May 5, and entered the clinic on May 24. The patient was symptom-free until November, when an abscess developed in the previous scar; she entered the hospital on November 7 and

remained until Jan. 5, 1931. After her discharge, she was symptom-free until October 1, when another abscess developed in the laparotomy scar. She entered the hospital on Octboer 23, and two abscesses were incised and drained; during the year of 1932 she entered the hospital twice with small abscesses in the previous scars and continued to have pain referable to the upper regions of the abdomen. She was last seen on Oct. 7, 1932, at which time she was having some epigastric discomfort.

The history is the most important aid to a diagnosis of chronic pancreatitis in the advanced stages. The patient usually says that his pain is more severe than at the onset of his complaints, and that the dull discomfort that he had when the ulcer was first diagnosed has disappeared. Food gives little relief, and he is awake several hours at night from pain, and frequently requires sedatives before he can sleep. The pain radiates directly through to the lumbar region and is usually felt on both the right and left sides of the spine. Physical examination reveals epigastric tenderness and a tenderness over the lumbar region which is equally marked on the right and left sides of the spine; the results of physical examination are otherwise negative. The routine laboratory work helps little in the prognosis of the course of ulcers. We used the amylase test of the blood serum according to Elman's method,[3] and the lipase test of the serum according to Cherry and Crandall's [4] method, in the hope of detecting cases of early chronic pancreatitis before the ulcer symptomatology had changed; it was hoped that with the infection and fibrosis of the pancreas the amylase and lipase would be constantly reduced in patients suffering from an associated pancreatitis, but our results were extremely variable and of no clinical significance; after using the tests on forty patients, we discontinued using them. While carrying out experiments on dogs in which we ligated the pancreatic ducts to produce thyroid changes, we studied the amylase and lipase of the blood of fifteen of these animals at weekly intervals until they died. The average life was four weeks, but some died within two weeks, while others lived eight weeks. Even in those animals in which a complete fibrosis of the pancreas developed, the results of the tests were most variable and could not be of clinical significance.

The selection of the time to operate in a case of peptic ulcer is of extreme importance. It is generally admitted that the results of operating early are unsatisfactory, regardless of the type of operation per-

3. Elman, Robert; Arneson, Norman, and Graham, E. A.: Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease, Arch. Surg. **19**:943 (Dec. pt. 1) 1929.

4. Cherry, I. S., and Crandall, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood after Pancreatic Injury, Am. J. Physiol. **100**:266 (April) 1932.

formed, while if the patient has suffered from the ulcer for a number of years, the results are more satisfactory following any operative procedure. The claim that the good results in cases of long standing come from some protective enzyme that develops in the blood and prevents marginal ulcers is mere speculation. I know, however, that operations thirty years ago gave satisfactory results. During the past ten years, in which patients have been referred for operation much sooner after the onset of symptoms, the surgical results have been generally unsatisfactory.

From clinical observations, it would seem that when a patient reveals the development of an associated pancreatitis, he ceases to present a medical problem; he should be operated on. To make the diagnosis of associated pancreatitis one must rely on the change in the pain symptomatology and on the clinical finding of tenderness over the regions of the kidneys with epigastric tenderness. After the infection of the pancreas has developed, delay in the operative treatment offers a more unfavorable prognosis.

I am aware of the emphasis that has been placed on cholecystitis as an etiologic and complicating factor in ulcers, but the more clinical and operative experience that I have with ulcers, the more I am impressed that there is only a slight relationship, either etiologic or symptomatic, between diseases of the biliary tract and peptic ulcers. The finding of an enlarged, firm pancreas, with the duodenum or the pyloric end of the stomach adherent to the gland, is of much more clinical significance and is a true indication for operative intervention. The indications that have been given for operating on ulcers, namely, a penetrating ulcer, a gastric ulcer, a pyloric obstruction, a gross hemorrhage and previous medical treatment, unless advanced by a competent internist, are not true indications for recommending surgery; the one indication is persistent pain that cannot be relieved by any method of medical care. The pain is usually due to an associated pancreatitis and is of a different character from that encountered in the early course of the disease. In 233 autopsies, Hurst and Stewart [5] found the pancreas forming the floor of the ulcer in 24.5 per cent of the cases, and the liver in 4.2 per cent; they also found in 183 partial gastrectomies that the pancreas formed the floor in 19.5 per cent and the liver in 1.5 per cent of the cases. With the ulcer and the pancreas in direct contact in such a high percentage of the cases, one would expect, clinically, to have a chronic infection of the pancreas which would alter the ulcer symptomatology, and that is what my associates and I have encountered.

5. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcers, New York, Oxford University Press, 1929, pp. 106 and 189.

From the study of our cases it is seen that chronic pancreatitis is a real indication for operating on a patient with an ulcer, as it is a condition that cannot be cured by medical care. The difficulty is in diagnosing the condition in its early stage; one has been forced to rely chiefly on the history and physical findings, as the routine laboratory studies are of little aid. In a previous paper [6] I reported the laboratory observations in 141 cases, namely, the complete blood counts, the results of gastric analyses, the results of chemical examination of the blood, including determinations of the urea, nonprotein nitrogen, sugar, creatinine, chlorides, calcium and phosphorus, and the results of Wassermann tests and of urinalyses; in none of these cases was the laboratory work of any aid in prognosticating the course of either gastric or duodenal ulcer.

COMMENT

It is obvious to every one who has had experience in treating patients with ulcers that there are spontaneous remissions with freedom from pain for weeks, months and years; this makes it extremely difficult to evaluate the results from either medical or surgical treatment unless the patients are seen at frequent intervals and observed over an indefinite period.

When chronic pancreatitis is associated with ulcer, the sooner the diagnosis is made and the patient operated on, the better the chances for a good prognosis. So far there have been no accurate laboratory methods of making such a diagnosis, and one has been forced to rely on clinical findings in arriving at such a conclusion. Determinations of the amylase of the duodenal contents are now being made and may aid in detecting early chronic pancreatitis; if so, one will be in a position to select with much more accuracy the patients that need to be operated on. This may remove from the internist's care those patients in whom he cannot hope for a good result from medical treatment and turn over to the surgeon those for whom there will be a good prognosis following operation. It will eliminate operations on patients who may respond permanently to conservative treatment, and diminish the incidence of that serious complication, gastrojejunal ulcer, which follows too frequently gastro-enterostomy and occasionally subtotal gastrectomy.

130 East Seventy-Ninth Street.

6. Hinton, J. W.: The Significance of Laboratory Studies in Gastric and Duodenal Ulcers, Am. J. Surg. 17:25 (July) 1932.

DIGESTION OF BONE BY LARVAE OF PHORMIA REGINA

ITS RELATIONSHIP TO BACTERIA

I. H. MASERITZ, M.D.

Assistant Orthopedic Surgeon, Department of Surgery, Sinai Hospital

BALTIMORE

The use of living maggots as a therapeutic measure in osteomyelitis was introduced [1] by Baer in 1929. He found that this treatment brought about early complete healing of infections of the bone that had been resistant to other forms of accepted therapy. The cause of this rapid healing was debated by Baer, but remained an unsolved problem in his mind. He felt that the end-results were possibly due to the ingestion of dead tissue by the maggots or to the liberation of an enzyme. He mentioned the possibility of extracting some active substance or enzyme the use of which might replace the application of living maggots to wounds. Unfortunately, he was unable to investigate these problems, and a continuation of his work would seem to be well worthy of consideration. Since this subject entails numerous problems requiring various steps of investigation, it was felt that a study on larval digestion would prove a necessary and interesting prelude.

Fabre (1894) in his study of the green bottle fly observed rapid liquefaction of coagulated albumin in the presence of maggots. This he attributed to an active pepsin secreted by the larvae. Guyénot (1906-1907) reinvestigated this problem and made various extracts of maggots and of their salivary glands, but failed to secure liquefaction or digestion of proteins, carbohydrates or fats. He was able, however, to isolate Micrococcus flavus-liquefaciens, which he showed was capable of liquefying protein, and he attributed the digestive changes in the larvae to the action of this organism. Bogdanow (1906-1908) confirmed the findings of Guyénot. Wollman (1911) repeated the experiments of Bogdanow, and found that he was able to raise larvae aseptically by tyndallizing mediums instead of autoclaving them; he felt that coagulation made the mediums indigestible, and that bacteria were not the cause of digestion. Baer (1931) was able to raise maggots aseptically by feeding them a medium of beef, liver and yeast. The problem of aseptic growth has been dealt with and confirmed by other workers. Of further interest is the demonstration by Weinland (1906) of the digestion of fibrin in the excreta of the larvae of Calliphora. Hobson

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1. For the history of the therapeutic application of maggots, antedating Baer's work, see Goldstein (1931) and Baer (1931).

(1931) showed, among other findings, the presence of a proteolytic
enzyme in the excreta and intestines of the larvae of Lucilia sericata.
The presence of enzymes capable of independent digestion has there-
fore been demonstrated in two species of larvae. Hobson has shown
that the proteolytic enzymes present in Lucilia sericata can digest
gelatin, elastin and white fibrous tissue collagen, but in view of the
fact that no study was made on the digestion of bone, I determined to
investigate the question of digestion of bone by larvae.
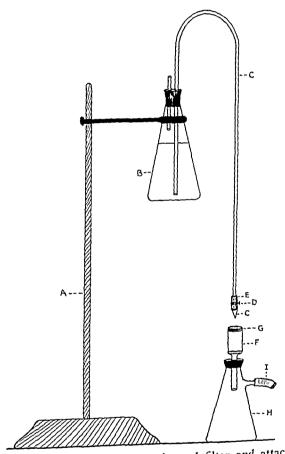
Fig. 1.—Diagrammatic sketch showing sintered filter and attachment of flask:
A, stand; *B*, flask for water; *C*, glass tubing; *D*, screw clamp; *E*, rubber tubing;
F, sintered filter; *G*, gauze covering filter; *H*, suction flask, and *I*, rubber tubing
to vacuum.

PRELIMINARY PREPARATIONS

Extraction of Enzymes from the Excreta of Larvae.—The methods for the
extraction of enzymes are taken from those used by Wigglesworth and later by
Hobson.

The maggots used in this work were pure strains of Phormia regina. Attempts
were made to raise larvae on Baer's medium, under sterile as well as under non-
sterile conditions. Maggots readily reached full growth on this food, but from
50 to 60 per cent of the larvae were dead at the end of forty-eight hours. Similar

results were obtained by raising the maggots on calf and hog brains. Extremely rapid liquefaction occurred in these mediums, and it was felt that toxic metabolic products were produced which caused destruction of the larvae. Beef, however, was found to be a very favorable medium for raising larvae under nonsterile conditions. Single strips of fresh lean beef, about 4 by 3 by 2 inches (10 by 7.5 by 0.5 cm.), were placed in a series of urine flasks. Approximately 100 maggots diluted with 2 cc. of distilled water were added to each flask. The mouths of the bottles were then plugged with cotton and the larvae incubated at 37 C. for forty-eight hours. At the end of this time the maggots were washed from the meats and bottles, distilled water being used, into a filter covered with a 60 mesh wire screen. Washings were continued until the filtrate was returned clear. The maggots were then placed over a sintered filter (fig. 1) covered with several layers of gauze. About 800 maggots were used during each period of extraction. This filter was then connected to a vacuum suction tube passing into the incubator. The suction, by disturbing the maggots, stimulated activity, whereas its absence admitted abnormal pupation. Distilled water was slowly dripped over the larvae and collected in the suction flask. An average of 30 cc. was collected during a period of five hours. The excreta consisted of a dark brown liquid suspension having an average hydrogen ion concentration of p_H 8.

Preparation of Bone.—Bone from human ribs was prepared by being scraped free from foreign tissues. Two preparations were made, one consisting of firm compact cortical bone and the other of finely ground bone. The preparations were completely dehydrated, well washed and again dehydrated. The cortical portions were made up into strips weighing 25 mg. each.

Controls.—The excreta were divided into two portions. One was left unaltered, while the other was heated over a water bath at 100 C. for five minutes. The first will be designated as unchanged excreta; the second, as heated excreta.

DIGESTIVE ACTION OF LARVAL EXCRETA

To 1 cc. portions of the unchanged excreta were added fixed amounts of bone. The cortical portions, as described, weighed 25 mg. each; 10 mg. of ground bone was used in each of these tests. Two controls were used; one consisted of heated excreta and bone and the other of unchanged excreta, to which no material was added. Small portions of thymol were added to all. Digestion was determined by loss of weight and increase in formaldehyde titrations. When ground bone was used, final determinations were calculated by the increase in formaldehyde titrations alone. All results were expressed in milligrams or fractions thereof or in cubic centimeters of hundredth-normal sodium hydroxide. All preparations were incubated at 37 C. for twenty-four hours. Digestion of ground bone occurred, as was evidenced by increase in formaldehyde titrations. In all cases, when whole cortical bone was used no changes resulted (table 1).

It is evident from these findings that the excreta of the larvae of Phormia regina contain an enzyme capable of digesting the organic portion of bone. Further studies, therefore, were made on ossein prepared from human ribs. All foreign tissue and the cancellous portion

of the bone were removed. The remaining cortical portions of the bone were then treated with 10 per cent hydrochloric acid for several days, well washed in distilled water, cut into strips and dehydrated. The average weight of the strips in a completely dehydrated state was 25 mg. A preliminary study was then made of the digestion of ossein by the excreta, and final calculations were determined by loss of weight and formaldehyde titrations. Controls were used as described in the experiments with whole bone. All mixtures were incubated at 37 C.

TABLE 1.—*Results of Experiments with Cortical and Ground Bone*

	Loss of Weight, Mg.	Final Titrations, Cc. of Hundredth-Normal NaOH
Experiment 1		
Cortical bone plus unchanged excreta.............	0	0
Cortical bone plus heated excreta.................	0	0
Ground bone plus unchanged excreta.............	—	0.4
Ground bone plus heated excreta.................	—	0
Unchanged excreta (control).....................	—	—
Experiment 2		
Cortical bone plus unchanged excreta.............	0	0
Cortical bone plus heated excreta.................	0	0
Ground bone plus unchanged excreta.............	—	0.32
Ground bone plus heated excreta.................	—	0
Unchanged excreta (control).....................	—	—
Experiment 3		
Cortical bone plus unchanged excreta.............	0	0
Cortical bone plus heated excreta.................	0	0
Ground bone plus unchanged excreta.............	—	0.34
Ground bone plus heated excreta.................	—	0
Unchanged excreta (control).....................	—	—
Experiment 4		
Cortical bone plus unchanged excreta.............	0	0
Cortical bone plus heated excreta.................	0	0
Ground bone plus unchanged excreta.............	—	0.46
Ground bone plus heated excreta.................	—	0
Unchanged excreta (control).....................	—	—
Experiment 5		
Cortical bone plus unchanged excreta.............	0	0
Cortical bone plus heated excreta.................	0	0
Ground bone plus unchanged excreta.............	—	0.36
Ground bone plus heated excreta.................	—	0
Unchanged excreta (control).....................	—	—

for twenty-four hours. Both decrease in weight and increase in formaldehyde titration occurred, showing digestion of ossein. All the controls gave negative results. The work was repeated, and the calculations are given in table 2.

Ssadikow (1927) isolated a collagenase from ox pancreas. He showed that kaolin absorbed the collagenase, while charcoal had no effect. Hobson (1931) repeated this work with maggots. He prepared white fibrous tissue collagen from catgut and treated it with the excreta of Lucilia sericata. After a series of experiments, he concluded that the enzyme acting on collagen, a substance similar to commercial gelatin, was entirely different from the one that digested gelatin. Bone collagen, according to Richard and Gies, possesses a chemical formula which differs slightly from that of tendon collagen; hence, it was felt that

the enzyme digesting bone collagen might prove to be specific for this substance only, and tests were instituted.

Since the determination of a collagenase depends on comparative study with other proteolytic enzymes and in view of the fact that no previous work had demonstrated the presence of such enzymes in the larvae of Phormia regina, it was found necessary to make preliminary studies.

Collagen was prepared from catgut, well washed and dehydrated. Commercial gelatin in a 5 per cent solution was used for simple proteolytic determinations. About 25 mg. of catgut and 1 cc. portions of gelatin were added to 1 cc. quantities of excreta. Controls, as previ-

TABLE 2.—*Results of Experiments with Ossein*

	Loss of Weight, Mg.	Increase in Formaldehyde Titration, Cc. of Hundredth-Normal NaOH
Experiment 1		
Ossein plus unchanged excreta....................	3.1	0.56
Ossein plus heated excreta......................	0	0
Unchanged excreta (control).....................	—	—
Experiment 2		
Ossein plus unchanged excreta....................	2.8	0.4
Ossein plus heated excreta......................	0	0
Unchanged excreta (control).....................	—	0
Experiment 3		
Ossein plus unchanged excreta....................	3.2	0.42
Ossein plus heated excreta......................	0	0
Unchanged excreta (control).....................	—	—
Experiment 4		
Ossein plus unchanged excreta....................	2.2	0.36
Ossein plus heated excreta......................	0	0
Unchanged excreta (control).....................	—	—
Experiment 5		
Ossein plus unchanged excreta....................	3.5	0.52
Ossein plus heated excreta......................	0	0
Unchanged excreta (control).....................	—	—

ously described, were used, and thymol was added to all. The digestion of catgut was determined by loss of weight and by formaldehyde titrations, while the digestion of gelatin was determined by formaldehyde titrations alone. Repeated experiments showed the presence of proteolytic enzymes which were capable of digesting both catgut and gelatin.

COMPARATIVE STUDY OF PROTEOLYTIC ENZYMES AND ATTEMPT TO EXTRACT A COLLAGENASE SPECIFIC FOR BONE

The bone collagen (ossein) used in this work was subjected to 25 per cent loss of weight by preliminary digestion so as to eliminate osseoalbuminoid, osseomucoid and the small portions of gelatin that might have been converted by previous contact with hydrochloric acid. In the same manner catgut was also subjected to predigestion.

Excreta were collected in the usual manner, and 6 cc. portions were treated, respectively, with 1 Gm. of animal charcoal and 1 Gm. of

kaolin. The tubes were shaken at frequent intervals for one-half hour and the contents filtered. To 1 cc. portions of the treated excreta were added catgut, bone collagen and 1 cc. portions of 5 per cent gelatin. Similar quantities were added to 1 cc. portions of unchanged excreta and heated controls. Portions of unchanged excreta (1 cc.) to which no material was added were used as basic controls for formaldehyde titrations. Thymol was added in each case. Incubations were carried out for forty-eight hours at 37 C. Digestion was determined by loss of weight when catgut or bone collagen was concerned, while formaldehyde titrations were used to determine the digestion of gelatin.

TABLE 3.—*Results of Experiments with Charcoal and Kaolin*

	Catgut Digested; Loss of Weight, Mg.	Bone Collagen Digested; Loss of Weight, Mg.	Gelatin Digested; Increase in Formaldehyde Titrations, Cc.
Preparation 1			
1. Excreta unchanged	3.5	3.0	1.4
2. Excreta treated with charcoal	3.1	1.5	0.9
3. Excreta treated with kaolin...	3.1	1.6	0.8
4. Heated controls	0	0	0
Preparation 2			
1. Excreta unchanged	4.2	3.5	1.6
2. Excreta treated with charcoal	2.1	2.4	1.4
3. Excreta treated with kaolin...	4.2	3.2	1.4
4. Heated controls	0	0	0
Preparation 3			
1. Excreta unchanged	3.4	3.15	1.2
2. Excreta treated with charcoal	2.9	3.05	0.8
3. Excreta treated with kaolin...	2.0	2.9	0.9
4. Heated controls	0	0	0
Preparation 4			
1. Excreta unchanged	3.3	3.4	1.4
2. Excreta treated with charcoal	2.85	3.0	1.0
3. Excreta treated with kaolin...	3.1	3.7	0.8
4. Heated controls	0	0	0
Preparation 5			
1. Excreta unchanged	3.2	3.1	1.8
2. Excreta treated with charcoal	2.8	2.5	1.0
3. Excreta treated with kaolin...	1.6	2.4	1.2
4. Heated controls	0	0	0

Careful study of the findings shown in table 3 will prove absorption of enzymes by kaolin and charcoal. These absorptive changes are present when catgut, bone collagen or gelatin is used. Furthermore, there is no evidence of specific absorption. Ssadikow (1927) found that kaolin completely absorbed the enzyme capable of digesting collagen, and further found that no changes occurred when this enzyme was treated with charcoal. It is therefore evident that the presence of a separate enzyme capable of digesting either catgut or bone collagen was not demonstrated. The changes found in this work also differ from those described by Hobson. From the findings it may be concluded that the proteolytic enzymes extracted from the excreta of Phormia regina are capable of digesting collagen, ossein and gelatin and are in all probability the same specific enzymes.

ORIGIN OF THE PROTEOLYTIC ENZYMES

Action of Emulsions of Intestinal Tracts and Salivary Glands on Bone Collagen.—The intestinal tracts and salivary glands of 80 fed larvae were isolated with the aid of a dissecting microscope. Each material was well emulsified and diluted to 10 cc. with 50 per cent glycerin. Portions containing 5 cc. of both the intestinal and the salivary emulsion were heated over a water bath at 100 C. for five minutes. The emulsions were divided into 1 cc. portions, and thymol was added. Human bone collagen was added to each, and incubations were carried on for twenty-four hours at 37 C. The collagen was then removed, well washed, dehydrated and reweighed. Digestion was determined by loss of weight as compared with absence of change in the heated con-

TABLE 4.—*Experiments with Intestinal and Salivary Emulsions*

	Mg. Collagen Digested
Experiment 1	
Bone collagen plus unchanged intestinal emulsion..........................	3.9
Bone collagen plus heated intestinal emulsion.............................	0
Experiment 2	
Bone collagen plus unchanged intestinal emulsion..........................	3.1
Bone collagen plus heated intestinal emulsion.............................	0
Experiment 3	
Bone collagen plus unchanged intestinal emulsion..........................	3.7
Bone collagen plus heated intestinal emulsion.............................	0
Experiment 4	
Bone collagen plus unchanged intestinal emulsion..........................	4.2
Bone collagen plus heated intestinal emulsion.............................	0
Experiment 5	
Bone collagen plus unchanged intestinal emulsion..........................	3.1
Bone collagen plus heated intestinal emulsion.............................	0

trols. Collagen was digested by the intestinal emulsions, but no changes were present in any of the gland preparations (table 4).

It is evident, therefore, that the enzymes found in the excreta are passed from the intestinal tracts of the larvae. It is not assumed, however, that the negative action of the gland emulsions definitely eliminates these tissues as the possible source of origin of proteolytic enzymes. There are many factors to be weighed, and in view of the limited literature and the differences in opinion concerning the salivary glands, it will be necessary that this problem be investigated further before a definite conclusion can be drawn.

The findings in table 4 are of further interest when compared with those of Hobson on the larvae of Lucilia sericata. He found that the collagenase was not present in emulsions made from the intestinal tracts of fed larvae, and further that the collagenase in intestinal emulsions of starved larvae was present only to a moderate degree when compared with the action of excreta. A comparative study of tables 4 and 2

shows that intestinal emulsions of fed larvae are more capable of digesting ossein than similar quantities of excreta. Since Hobson used catgut in his experiments, we proceeded to investigate the action of intestinal emulsions of fed larvae (Phormia regina) on this substance. The emulsions were found to digest catgut equally well and, when compared with the excreta, showed greater activity.

Action of Bacteria on Bone Collagen.—Since the larvae used for the preceding work were raised on nonsterile mediums, it seemed necessary to consider the possibility that bacteria might play some part in the process of digestion. Repeated cultures and smears made directly from intestinal contents always showed the presence of a gram-negative bacillus and a gram-negative coccus. The bacillus was of the proteus group while the coccus proved to be M. flavus-liquefaciens, both of which had been demonstrated by previous workers. At no time could other organisms be isolated, other than specific bacteria, when these were inoculated on sterile maggot mediums.

Since all maggots used in this work were removed from nonsterile mediums after forty-eight hours' growth, cultures of these bacteria were grown on agar slants for two days and then suspended in physiologic solution of sodium chloride. To 1 cc. portions of forty-eight hour suspensions bone collagen was added. Controls of physiologic solution of sodium chloride were used. Since thymol had been used in each previous experiment, small amounts were added to all the portions. No digestion of bone collagen occurred. In order to check these results, bone collagen was treated with alcohol for one week, well washed with sterile water and then placed in a sterile medium containing feeding larvae. Examination after forty-eight hours showed digestion of bone collagen. Bacteria, therefore, played no rôle in the preceding experiments.

STABILITY OF THE ENZYME

A brief study was made to determine the stability of the enzyme. Intestinal emulsions were prepared, eight intestines being used for each cubic centimeter of saline solution. Equal portions of glycerin were added to half of the aliquots and thymol to all. The emulsions were

TABLE 5.—*Experiments to Determine Stability of the Enzyme*

	Mg. of Bone Collagen Digested
Bone collagen plus excreta plus thymol after 24 hours	2.8
Bone collagen plus excreta plus thymol plus glycerin after 24 hours	3.2
Bone collagen plus excreta plus thymol after 48 hours	2.2
Bone collagen plus excreta plus thymol plus glycerin after 48 hours	3.1
Bone collagen plus excreta plus thymol after 72 hours	1.9
Bone collagen plus excreta plus thymol plus glycerin after 72 hours	3.1
Bone collagen plus excreta plus thymol after 1 week	1.75
Bone collagen plus excreta plus thymol plus glycerin after 1 week	2.5

incubated, and after twenty-four, forty-eight and seventy-two hours and one week bone collagen was added to both glycerin and plain emulsions. Further incubations were then carried out for forty-eight hours at 37 C. The results are given in table 5.

A study of table 5 shows that the enzyme possesses a fair amount of stability. Guyénot (1907) showed that maggots were capable of ingesting only microscopic particles, and it would therefore appear that stability of enzymes would be a necessity for the existence of larval life.

PROTEOLYTIC ACTIVITY AT VARIOUS HYDROGEN ION CONCENTRATIONS

It was felt to be of value and of interest to determine the concentration at which proteolytic activity reached a maximum. Emulsions were made with five intestinal tracts to each cubic centimeter of buffer solution at various concentrations as shown in figure 2. These emulsions were corrected when necessary, and equal portions of ossein were added to each. The results are presented in figure 2.
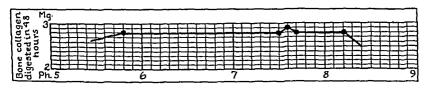
Fig. 2.—Chart showing proteolytic activity at various hydrogen ion concentrations.

The findings failed to reveal an appreciable point of maximum activity, but showed a rather wide range with virtually no variation. At p_H 7.5 there was an increase in the digestion of collagen of 0.1 mg., while below p_H 5.8 and above p_H 8.2 the activity decreased. This wide range apparently would permit the larvae to adapt themselves to an average medium.

SUMMARY OF OBSERVATIONS IN FOREGOING SECTIONS, WITH COMMENT

The intestines of the larvae of Phormia regina excrete a proteolytic enzyme capable of digesting bone. The digestion occurs essentially on ossein, the organic portion of the bone. No attempt was made to determine the ultimate fate of the inorganic salts; since this matter would involve an extensive investigation, the subject was left open for further research. The enzyme, which can also be extracted from the excreta of the larvae, shows fair stability and is capable of maximum activity over a wide range. Digestion of gelatin and collagen derived from white fibrous tissue has also been demonstrated, but a specific enzyme for each of the substances could not be found.

It is of interest to note that Shinoda (1928) showed digestion of collagen by the gastric juice of the crawfish (Astacus) but felt that, with the present knowledge of enzymes, an attempt to extract a specific agent was not feasible. He, too, found that the activity of the enzyme occurred over a wide range with little evidence of a maximum point of digestion.

RELATIONSHIP OF MAGGOTS TO BACTERIA

For years it was felt that bacteria played an essential part in larval digestion. Baumberger (1919) stated that bacteria were an important source of food, while Portier (1919) considered them a source of vitamins for maggots. My previous study of digestion obviates the necessity for any further preliminary review of the literature other than a consideration of several factors. It has been proved that bacteria are not necessary to the growth of larvae. Duncan (1926) and other workers have demonstrated bacterial destruction by the intestines of maggots. Whether maggots are capable of destroying bacteria by virtue of immunity or by digestion is open for consideration, since no specific evidence has thus far been given relating to this subject. Livingston (1932) felt that an active principle was present which was capable of destroying bacteria, and, furthermore, he believed that this active substance could be extracted by making emulsions of mashed maggots. No experimental evidence was given other than the ingestion of bacteria by larvae and the clinical evidence of cures. The question of the relationship of maggots to bacteria is therefore open for further investigation.

Procedure.—Maggots were cultivated by aseptic means, the Baer beef, liver and yeast medium being employed. About 200 maggots were emulsified with physiologic solution of sodium chloride to make a liquid suspension. Twenty-four hour growths of Staphylococcus aureus, Pneumococcus, the typhoid bacillus, Bacillus proteus and Micrococcus flavus-liquefaciens were suspended in physiologic solution of sodium chloride, very dilute suspensions being made. The staphylococcus was obtained from the wound of an operation for osteomyelitis, while B. proteus and the micrococcus were taken from an intestinal smear of maggots. Dilutions as high as 1:16 were made of the maggot emulsions. The usual routine bactericidal tests were performed with each type of bacterium mentioned, a saline control being used in every case. In each group 1 cc. of emulsion was mixed with 0.5 cc. of bacterial suspension, incubated at 37 C. for three hours, plated on agar and incubated for twenty-four hours, and the colonies were then counted. This work was repeated with sterile maggots raised on Baer's medium which had been inoculated with each of the organisms described, i. e., Staphylococcus in flask 1, Pneumococcus in flask 2, etc.

Results of both groups of experiments are given in tables 6 to 10.

A study of the results shows that emulsions of maggots are not bactericidal in action, but on the contrary favor bacterial growth.

TABLE 6.—*Bactericidal Tests with Emulsions of Maggots and Staph. Aureus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. S. aureus suspension......	1,280	1,620
Diluted 1:2 plus 0.5 cc. S. aureus suspension....	848	1,360
Diluted 1:4 plus 0.5 cc. S. aureus suspension......	800	820
Diluted 1:8 plus 0.5 cc. S. aureus suspension..................	496	670
Diluted 1:16 plus 0.5 cc. S. aureus suspension..................	380	500
1 cc. physiologic solution of sodium chloride plus 0.5 cc. S. aureus suspension	132	236
Experiment 2		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. S. aureus suspension.	1,440	1,280
Diluted 1:2 plus 0.5 cc. S. aureus suspension..	644	750
Diluted 1:4 plus 0.5 cc. S. aureus suspension., ...	779	648
Diluted 1:8 plus 0.5 cc. S. aureus suspension..................	416	307
Diluted 1:16 plus 0.5 cc. S. aureus suspension..................	65	120
1 cc. physiologic solution of sodium chloride plus 0.5 cc. S. aureus suspension	84	96
Experiment 3		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. S. aureus suspension....................	1,318	1,414
Diluted 1:2 plus 0.5 cc. S. aureus suspension........	890	840
Diluted 1:4 plus 0.5 cc. S. aureus suspension..................	480	632
Diluted 1:8 plus 0.5 cc. S. aureus suspension................. ..	328	460
Diluted 1:16 plus 0.5 cc. S. aureus suspension..................	214	310
1 cc. physiologic solution of sodium chloride plus 0.5 cc. S. aureus suspension	57	84

TABLE 7.—*Bactericidal Tests with Emulsions of Maggots and B. Typhosus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. B. typhosus suspension.................	1,136	1,158
Diluted 1:2 plus 0.5 cc. B. typhosus suspension.................	794	864
Diluted 1:4 plus 0.5 cc. B. typhosus suspension.................	560	619
Diluted 1:8 plus 0.5 cc. B. typhosus suspension.................	500	420
Diluted 1:16 plus 0.5 cc. B. typhosus suspension.................	370	314
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	122	108
Experiment 2		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. B. typhosus suspension.................	690	940
Diluted 1:2 plus 0.5 cc. B. typhosus suspension.................	585	796
Diluted 1:4 plus 0.5 cc. B. typhosus suspension.................	480	598
Diluted 1:8 plus 0.5 cc. B. typhosus suspension.................	328	320
Diluted 1:16 plus 0.5 cc. B. typhosus suspension.................	214	116
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	57	72
Experiment 3		
Undiluted plus 0.5 cc. B. typhosus suspension.................	898	762
Diluted 1:2 plus 0.5 cc. B. typhosus suspension.................	772	372
Diluted 1:4 plus 0.5 cc. B. typhosus suspension.................	567	450
Diluted 1:8 plus 0.5 cc. B. typhosus suspension.................	328	274
Diluted 1:16 plus 0.5 cc. B. typhosus suspension.................	240	116
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	96	84

TABLE 8.—*Bactericidal Tests with Suspensions of Maggots and Pneumococcus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. pneumococcus suspension	630	670
Diluted 1:2 plus 0.5 cc. pneumococcus suspension	510	420
Diluted 1:4 plus 0.5 cc. pneumococcus suspension	379	400
Diluted 1:8 plus 0.5 cc. pneumococcus suspension	160	182
Diluted 1:16 plus 0.5 cc. pneumococcus suspension	46	91
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	58	84
Experiment 2		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. pneumococcus suspension	590	520
Diluted 1:2 plus 0.5 cc. pneumococcus suspension	360	412
Diluted 1:4 plus 0.5 cc. pneumococcus suspension	270	308
Diluted 1:8 plus 0.5 cc. pneumococcus suspension	200	168
Diluted 1:16 plus 0.5 cc. pneumococcus suspension	102	96
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	48	50
Experiment 3		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. pneumococcus suspension	412	390
Diluted 1:2 plus 0.5 cc. pneumococcus suspension	290	248
Diluted 1:4 plus 0.5 cc. pneumococcus suspension	200	172
Diluted 1:8 plus 0.5 cc. pneumococcus suspension	168	106
Diluted 1:16 plus 0.5 cc. pneumococcus suspension	38	52
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	86	80

TABLE 9.—*Bactericidal Tests with Suspensions of Maggots and B. Proteus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. B. proteus suspension	1,680	1,470
Diluted 1:2 plus 0.5 cc. B. proteus suspension	1,292	1,264
Diluted 1:4 plus 0.5 cc. B. proteus suspension	730	692
Diluted 1:8 plus 0.5 cc. B. proteus suspension	414	274
Diluted 1:16 plus 0.5 cc. B. proteus suspension	196	196
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	104	176
Experiment 2		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. B. proteus suspension	1,388	1,414
Diluted 1:2 plus 0.5 cc. B. proteus suspension	694	1,002
Diluted 1:4 plus 0.5 cc. B. proteus suspension	710	645
Diluted 1:8 plus 0.5 cc. B. proteus suspension	390	329
Diluted 1:16 plus 0.5 cc. B. proteus suspension	176	206
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	172	183
Experiment 3		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. B. proteus suspension	1,880	1,446
Diluted 1:2 plus 0.5 cc. B. proteus suspension	1,435	749
Diluted 1:4 plus 0.5 cc. B. proteus suspension	1,006	576
Diluted 1:8 plus 0.5 cc. B. proteus suspension	645	441
Diluted 1:16 plus 0.5 cc. B. proteus suspension	560	329
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	320	192

A preliminary study was now made of bacteria found in the intestinal tracts of the larvae of Phormia regina. B. proteus and M. flavus-liquefaciens, which have already been described, could be seen in abundance in intestinal smears. Grown maggots were placed on a sintered filter and covered with gauze. The larvae were washed with a slow stream of water which was continuously removed by a vacuum suction apparatus connected to a flask. In this manner the larvae were kept moist and active. Starvation was continued for a week, and each day the maggots that had survived the ordeal were

TABLE 10.—*Bactericidal Tests with Suspensions of Maggots and M. Flavus Liquefaciens*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension...	1,242	1,358
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension..	868	846
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	588	592
Diluted 1:8 plus 0.5 cc. Micrococcus finvus-liquefaciens suspension.	346	464
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	244	322
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	226	245
Experiment 2		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension...	1,300	1,106
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	864	1,650
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	792	549
Diluted 1:8 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	506	364
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	375	298
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	162	184
Experiment 3		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension...	870	1,012
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	644	804
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	328	658
Diluted 1:8 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	204	436
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	162	208
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	122	188

removed. At intervals, examinations were made of intestinal smears, but no gross evidence of decrease in bacteria could be noted. Further study was then made by emulsifying intestinal tracts which had been dissected from the maggots. About ten intestinal tracts were used to each cubic centimeter of physiologic solution of sodium chloride, and the solution was filtered through a Mandler filter. Bactericidal tests were made, the technic and organisms used being the same as those previously described. The results of these experiments were negative. Representative tests are recorded in table 11.

Further studies were then made, consisting of agglutination tests, both microscopic and macroscopic. Observations were also made for lytic changes. Emulsions were prepared of whole sterile maggots and contaminated maggots as described, i. e., maggots fed in mediums inocu-

lated with pure strains of Staphylococcus, Pneumococcus and other organisms, and emulsions of intestines. The emulsion of whole maggots was prepared by mashing 200 larvae and diluting with physiologic solution of sodium chloride, while ten intestinal tracts to each cubic centimeter of saline solution were used in the second preparation.

TABLE 11.—*Results of Bactericidal Tests with Emulsions of Larval Intestines and Bacteria Found in Larval Intestinal Tracts*

	Number of Colonies After 24 Hours' Incubation
Experiment 1	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. Staphylococcus aureus suspension...............	1,330
Diluted 1:2 plus 0.5 cc. Staphylococcus aureus suspension..............	1,012
Diluted 1:4 plus 0.5 cc. Staphylococcus aureus suspension..............	860
Diluted 1:8 plus 0.5 cc. Staphylococcus aureus suspension..............	488
Diluted 1:16 plus 0.5 cc. Staphylococcus aureus suspension.............	360
1 cc. physiologic solution of sodium chloride..............................	166
Experiment 2	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. pneumococcus suspension........................	1,160
Diluted 1:2 plus 0.5 cc. pneumococcus suspension.......................	876
Diluted 1:4 plus 0.5 cc. pneumococcus suspension.......................	648
Diluted 1:8 plus 0.5 cc. pneumococcus suspension.......................	412
Diluted 1:16 plus 0.5 cc. pneumococcus suspension......................	220
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	176
Experiment 3	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. B. typhosus suspension..........................	940
Diluted 1:2 plus 0.5 cc. B. typhosus suspension.........................	866
Diluted 1:4 plus 0.5 cc. B. typhosus suspension.........................	572
Diluted 1:8 plus 0.5 cc. B. typhosus suspension.........................	268
Diluted 1:16 plus 0.5 cc. B. typhosus suspension........................	138
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	100
Experiment 4	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. B. proteus suspension...........................	1,124
Diluted 1:2 plus 0.5 cc. B. proteus suspension..........................	910
Diluted 1:4 plus 0.5 cc. B. proteus suspension..........................	880
Diluted 1:8 plus 0.5 cc. B. proteus suspension..........................	574
Diluted 1:16 plus 0.5 cc. B. proteus suspension.........................	254
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	238
Experiment 5	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.......	728
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension......	712
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension......	426
Diluted 1:8 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension......	294
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.....	188
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	87

All emulsions were filtered through a Mandler filter. Portions (1 cc.) of very dilute suspensions of twenty-four hour bacterial growths were added to the emulsions and incubated for several hours at 37 C. Microscopic agglutination tests were made, 1 loopful of emulsion and 1 loopful of bacterial suspension being used. Observations were made for several hours, during which time the hollow ground slide suspensions were incubated as described. There was no evidence of definite agglutination or lysis (table 12).

TABLE 12.—*Tests for Agglutination and for Lysis of Bacteria by Emulsions of Whole Maggots Contaminated and Uncontaminated and by Emulsions of Their Intestines*

	Staphylococcus Aureus			Pneumococcus			B. Typhosus			B. Proteus			M. Flavus-Liquefaciens		
	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis
(1) Whole maggot emulsion	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Whole maggot emulsion	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Whole maggot emulsion	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Whole maggot emulsion	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Whole maggot emulsion	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Whole maggot emulsion	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
(2) Whole maggot emulsion treated with Staph. aureus	o	o	o	—	—	—	—	—	—	—	—	—	—	—	—
Same	o	o	o	—	—	—	—	—	—	—	—	—	—	—	—
Same	o	o	o	—	—	—	—	—	—	—	—	—	—	—	—
Same	o	o	o	—	—	—	—	—	—	—	—	—	—	—	—
(3) Whole maggot emulsion treated with pneumococcus	—	—	—	o	o	o	—	—	—	—	—	—	—	—	—
Same	—	—	—	o	o	o	—	—	—	—	—	—	—	—	—
Same	—	—	—	o	o	o	—	—	—	—	—	—	—	—	—
Same	—	—	—	o	o	o	—	—	—	—	—	—	—	—	—
(4) Whole maggot emulsion treated with B. typhosus	—	—	—	—	—	—	o	o	o	—	—	—	—	—	—
Same	—	—	—	—	—	—	o	o	o	—	—	—	—	—	—
Same	—	—	—	—	—	—	o	o	o	—	—	—	—	—	—
Same	—	—	—	—	—	—	o	o	o	—	—	—	—	—	—
(5) Whole maggot emulsion treated with B. proteus	—	—	—	—	—	—	—	—	—	o	o	o	—	—	—
Same	—	—	—	—	—	—	—	—	—	o	o	o	—	—	—
Same	—	—	—	—	—	—	—	—	—	o	o	o	—	—	—
Same	—	—	—	—	—	—	—	—	—	o	o	o	—	—	—
(6) Whole maggot emulsion treated with M. flavus-liquefaciens	—	—	—	—	—	—	—	—	—	—	—	—	o	o	o
Same	—	—	—	—	—	—	—	—	—	—	—	—	o	o	o
Same	—	—	—	—	—	—	—	—	—	—	—	—	o	o	o
Same	—	—	—	—	—	—	—	—	—	—	—	—	o	o	o
(7) Intestinal emulsion	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Same	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Same	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
Same	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o

The final study was devoted to the possibility of digestion of bacteria by larvae. Emulsions were made of ten intestinal tracts and 1 cc. of physiologic solution of sodium chloride. Dilute saline suspensions were

TABLE 13.—*Tests for Digestion of Bacteria by Emulsions of Larval Intestines*

	Increase in Formaldehyde Titration, Cc. Hundredth-Normal NaOH
Experiment 1	
(1) 1 cc. unchanged intestinal emulsion plus 1 cc. S. aureus suspension..........	0
1 cc. heated intestinal emulsion plus 1 cc. S. aureus suspension..............	0
1 cc. unchanged control	—
(2) 1 cc. unchanged intestinal emulsion plus 1 cc. S. aureus suspension..........	0
1 cc. heated intestinal emulsion plus 1 cc. S. aureus suspension..............	0
1 cc. unchanged control	—
(3) 1 cc. unchanged intestinal emulsion plus 1 cc. S. aureus suspension..........	0
1 cc. heated intestinal emulsion plus 1 cc. S. aureus suspension..............	0
1 cc. unchanged control	—
Experiment 2	
(1) 1 cc. unchanged intestinal emulsion plus 1 cc. B. typhosus suspension......	0
1 cc. heated intestinal emulsion plus 1 cc. B. typhosus suspension..........	0
1 cc. unchanged control	—
(2) 1 cc. unchanged intestinal emulsion plus 1 cc. B. typhosus suspension......	0
1 cc. heated intestinal emulsion plus 1 cc. B. typhosus suspension..........	0
1 cc. unchanged control	—
(3) 1 cc. unchanged intestinal emulsion plus 1 cc. B. typhosus suspension......	0
1 cc. heated intestinal emulsion plus 1 cc. B. typhosus suspension..........	0
1 cc. unchanged control	—
Experiment 3	
(1) 1 cc. unchanged intestinal emulsion plus 1 cc. B. proteus suspension........	0
1 cc. heated intestinal emulsion plus 1 cc. B. proteus suspension............	0
1 cc. unchanged control	—
(2) 1 cc. unchanged intestinal emulsion plus 1 cc. B. proteus suspension........	0
1 cc. heated intestinal emulsion plus 1 cc. B. proteus suspension............	0
1 cc. unchanged control	—
(3) 1 cc. unchanged intestinal emulsion plus 1 cc. B. proteus suspension........	0
1 cc. heated intestinal emulsion plus 1 cc. B. proteus suspension............	0
1 cc. unchanged control	—
Experiment 4	
(1) 1 cc. unchanged intestinal emulsion plus 1 cc. M. flavus-liquefaciens susp...	0
1 cc. heated intestinal emulsion plus 1 cc. M. flavus-liquefaciens suspension	0
1 cc. unchanged control	—
(2) 1 cc. unchanged intestinal emulsion plus 1 cc. M. flavus-liquefaciens susp...	0
1 cc. heated intestinal emulsion plus 1 cc. M. flavus-liquefaciens suspension	0
1 cc. unchanged control	—
(3) 1 cc. unchanged intestinal emulsion plus 1 cc. M. flavus-liquefaciens susp...	0
1 cc. heated intestinal emulsion plus 1 cc. M. flavus-liquefaciens suspension	0
1 cc. unchanged control	—
Experiment 5	
(1) 1 cc. unchanged intestinal emulsion plus 1 cc. pneumococcus suspension....	0
1 cc. heated intestinal emulsion plus 1 cc. pneumococcus suspension.........	0
1 cc. unchanged control	—
(2) 1 cc. unchanged intestinal emulsion plus 1 cc. pneumococcus suspension....	0
1 cc. heated intestinal emulsion plus 1 cc. pneumococcus suspension.........	0
1 cc. unchanged control	—
(3) 1 cc. unchanged intestinal emulsion plus 1 cc. pneumococcus suspension....	0
1 cc. heated intestinal emulsion plus 1 cc. pneumococcus suspension.........	0
1 cc. unchanged control	—

made of Staph. aureus, the typhoid bacillus, Pneumococcus, B. proteus and M. flavus-liquefaciens. Quantities of 1 cc. of each were added to equal portions of intestinal emulsions, and a preliminary study of bacterial counting was attempted. No changes were noted, and the results were

not considered sufficiently accurate to record. Heavy twenty-four hour suspensions of bacteria in physiologic solution of sodium chloride were then added to intestinal emulsions, 1 cc. portions of each being employed. Thymol was added in each case, and controls as described were run in series. Digestion was determined by increase in formaldehyde titrations. All results were negative (table 13).

SUMMARY OF OBSERVATIONS IN FOREGOING SECTION

The work failed to reveal any bactericidal action, agglutination, lysis or digestion of bacteria and does not confirm the claims of previous workers.

CONCLUSIONS

1. The intestines and excreta of the larvae of Phormia regina contain proteolytic enzymes capable of digesting ossein, white fibrous tissue collagen and gelatin.

2. No specificity of enzymes could be demonstrated.

3. The enzymes are fairly stable, and the activity extends over a wide range, the optimum being from p_H 5.8 to p_H 8.2.

4. No bactericidal action, agglutination, lysis or digestion of bacteria could be detected.

2309 Eutaw Place.

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FIFTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

JOHN G. KUHNS, M.D.

EDWIN F. CAVE, M.D.

SUMNER M. ROBERTS, M.D.

AND

JOSEPH S. BARR, M.D.

BOSTON

JOSEPH A. FREIBERG, M.D.

CINCINNATI

JOSEPH E. MILGRAM, M.D.

NEW YORK

ROBERT I. STIRLING, M.D.

EDINBURGH, SCOTLAND

AND

PHILIP D. WILSON, M.D.

Advisory Editor

BOSTON

MISCELLANEOUS

Degeneration of Rib Cartilage.—Following Trauma: Bauer [25] reported a rare form of chondromalacia of the cartilages of the fourth and fifth ribs on the right side following a severe injury to this region. Because of pain, these cartilages were removed with complete relief from symptoms. Examination of the cartilage that was removed showed necrosis and degeneration which, the author believed, were the result of local vascular damage. Five similar lesions in the costal cartilages had been reported in the literature.

Morphologic Changes in the Wrist Joint After Removal of the Carpal Semilunar Bone.—Dietrich [26] studied the changes in the wrist joint after extirpation of the carpal semilunar bone for osteoporosis in 11 cases. He observed an ulnar displacement of the scaphoid and a narrowed articulation with the radius. The carpal bones had a decreased length in the axis of the limb, and the capitatum was

25. Bauer, C. D.: Ztschr. f. Chir. **239**:733, 1932.
26. Dietrich, H.: Arch. f. klin. Chir. **174**:146, 1933.

in a deeper position. External rotation and abduction were decreased. When only partial extirpation had been performed, partial regeneration often occurred.

Bipartite Carpal Navicular Bone.—Reporting a case found post mortem, Boyd [27] reconsidered the question of bipartite carpal navicular bone. The points differentiating this from a fracture of the navicular bone were taken to be: (1) absence of history of injury; (2) meagerness of physical signs; (3) roentgenographic appearance (in the congenital condition the cortex was uniform around the segments of the bone, while in the traumatic condition a broader, less sharply defined, dividing line was found), and (4) the possible bilateral presence of the congenital condition.

Stieda's Shadows on the Inner Aspect of the Femoral Condyles.—Andreesen [28] studied 28 cases of Pellegrini-Stieda's disease. He divided them into three groups according to the roentgenographic changes shown on the inner femoral condyle: 1. Cases showing a simple striplike shadow along the inner femoral condyle. This was observed in 11 cases, in all of which there was a typical history of injury to the meniscus. 2. Cases showing a flat, irregular, shell-like shadow with a much decreased calcium content in comparison with the first group. This was observed in 8 patients, 3 of whom had a severe contusion on the inner side of the knee; the other 5 had severe twisting injuries. 3. Cases showing shadows much larger than usual, irregular and extending upward with apparent attachment to the condyle. In this group (9 patients) the injury to the knee was more severe; in 3 there was a tear of the cruciate ligament and in 2 a complete tear of the internal lateral ligament. The end-results were much poorer in this third group. As a cause of these shadows, the author suggested a tear with subsequent hemorrhage and later calcification at the attachment of the adductor magnus. In group 3 an additional injury to the adjacent periosteum was postulated. All patients were in the third to the fifth decade. Immobilization symptomatically for the original injury with surgical measures when indicated was the treatment used. Study of cases for as long as six years showed little change in these roentgen shadows. Symptoms, when present, were accounted for by derangement in function caused by the original injury.

Posttraumatic Painful Osteoporosis.—Fontaine and Herrmann [29] advocated sympathectomy in cases of traumatic osteoporosis, a form of treatment carried out in Lerichel's clinic since 1924. The condition usually involved the bones of the hand or foot, and followed either

27. Boyd, G. I.: Brit. J. Surg. **20**:455, 1933.
28. Andreesen, R.: Arch. f. klin. Chir. **174**:162, 1933.
29. Fontaine, R., and Herrmann, L. G.: Ann. Surg. **97**:26, 1933.

slight injuries (strains or sprains) or more extensive injuries (fractures or dislocations). It was characterized by: (1) loss of motor function of the extremity, (2) characteristic (osteoporotic) changes in the roentgenogram, (3) vasomotor disturbance and (4) pain. Twenty-two cases were reported, including 9 cases involving the bones of the wrist, 7 cases involving the bones of the ankle and 3 cases involving the bones of the shoulder joint.

Nature and Treatment of So-Called Tennis Elbow.—Hohmann,[30] from his studies of tennis elbow, concluded that the primary cause was a periosteal tear. In roentgenograms a thickening could usually be observed over the lateral epicondyle. For treatment in the early cases, rest was advocated, usually with a plaster cast including the hand, with no stretching of the spastic muscles about the elbow or forearm. Diathermy was given but no massage. In the chronic cases, operative treatment was advised. A curved incision was carried down to the bone over the external epicondyle, and the extensor muscles were then pushed distally from their attachment, in this way removing the pull of the muscles on the previously injured periosteal area. Good results were reported in 15 cases in which this operation was performed.

Glycine Treatment of Progressive Muscular Dystrophy.—Kostakow and Slauck[31] studied the action of glycine in 7 persons with progressive muscular dystrophy as well as in 4 normal persons. They concluded that glycine played a rôle in muscular physiology similar to phosphatase and lactic acid. In muscular dystrophy the nature of the disease consisted in the inability of the body to metabolize creatine. By the addition of glycine, the muscular metabolism was improved and creatine metabolism was made more nearly normal. Through glycine therapy, the authors felt that new therapeutic possibilities were presented for the patients with progressive muscular dystrophy.

Gas Gangrene and Its Treatment.—Effkemann[32] reviewed 53 cases of gas gangrene in which treatment was given at the Rudolf Virchow Hospital between 1928 and 1931. Thirty-four of the patients recovered, 16 with amputation; 19 died, 3 after amputation. Bacillus welchii was found in almost every case, usually in combination with other anaerobes. The local death of tissue, presence of nonpathogenic anaerobes, alkali content of the wound and poor hemostasis all aided in producing gas gangrene. In experimental animals the author was unable to produce gas gangrene with pure cultures of B. welchii when the wound was left open, even when earth was added; sewing the wound often led to

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30. Hohmann, G.: München. med. Wchnschr. **80**:250 (Feb. 17) 1933.

31. Kostakow, S., and Slauck, A.: Deutsche med. Wchnschr. **59**:169 (Feb. 3) 1933.

32. Effkemann, G.: Arch. f. klin. Chir. **174**:1, 1933.

gas gangrene. Latent infections as shown in experimental animals might be activated by subsequent purulent infections. The best results were observed with large, repeated doses of a polyvalent serum. In addition, wide incision and packing with antiseptics were used. As antiseptics, solutions of potassium permanganate and surgical solution of chlorinated soda seemed best.

FRACTURES

Damage to the Knee Joint from Long-Continued Traction in Fractures of the Thigh.—Felsenreich [33] analyzed two groups of femoral fractures each comprising 30 cases. The first group was treated by traction applied through the tuberosities of the tibiae. The second group was treated by traction through the femoral condyles. The author's interest lay in the consideration of symptoms of the knee joint which so often followed long-continued traction through the joint. In 5 of the 30 patients on whom tibial traction was employed severe "traction injuries" developed, necessitating manipulation. At these attempts adhesions were demonstrable, particularly in the suprapatellar pouch. Only 3 of the 5 did well. The author stated that instability of the knee did not develop in this group, but that definite limitation of motion had appeared. The articular capsule was stretched; the delicate synovial lining also was stretched. Inflammatory evidences of pain and effusion appeared rapidly, and in a few weeks extensive adhesions were present in the joint. For these reasons Felsenreich felt that traction through the tibial tuberosities was undesirable and should never be persisted in more than from three to four weeks, even in cases in which no alternative to traction was advisable. He advised condylar traction wherever possible, and open reduction, when necessary, as the lesser of two evils.

[ED. NOTE.—The author, in attributing these disabilities to traction, seems to be overlooking the influence of prolonged immobilization.]

Treatment of Patellar Fractures and Posttraumatic Arthritis.— Of 57 patients with patellar fractures with separation of the fragments, 17 were treated conservatively and 40 were operated on by Frederick.[34] In 90 per cent of the cases in which operation was performed, normal or almost normal function was obtained, compared to less than 60 per cent of normal function in the nonoperative groups. In more than 50 per cent of the operative group, the result was perfect. Bony healing occurred proportionately three times as often in the operative group as in the nonoperative group. Arthritis appeared twice as often in the nonoperative as in the operative group. Frederick believed the

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33. Felsenreich, F.: Arch. f. klin. Chir. **174**:667, 1933.
34. Frederick, R.: Arch f. klin. Chir. **174**:747, 1933.

causes of the arthritis to be: (1) trauma, (2) hemarthrosis, (3) long immobilization of the joint and (4) poor union of the fracture.

Operation for Fracture of the Patella.—Ober [35] reported on a single case of transverse fracture of the patella which was repaired with a portion of the quadriceps tendon. The midportion of the quadriceps tendon was divided transversely approximately 4 inches above the superior border of the patella and split longitudinally, and the two pieces of tendon were dissected free down to the patella. These two tendinous strips were then passed through drill holes in the patella and sewed to the ligamentum patellae. The patella united solidly, and the patient obtained 85 per cent of flexion in approximately eight months' time.

Fractures of the Head and Neck of the Radius.—Fourteen cases of fracture of the proximal end of the radius in children were reported by Bohrer.[36] These cases from the Children's Fracture Clinic at Bellevue Hospital were seen during the past ten years and represented 3 per cent of all of the fractures about the elbow joint. From a study of these cases the author concluded that fractures of the head and neck of the radius in children should be treated conservatively unless there was marked displacement of the fragments; with marked displacement, early operation with replacement was preferable to resection. If resection was done, about 50 per cent would present synostosis of the radius and ulna several months after operation. Of 5 children operated on, 2 had full function permanently; 3 had complete function when discharged from the hospital, but over a period of several months rotation was lost because of productive periostitis followed by synostosis of the radius and ulna. Of the 9 patients treated conservatively, 3 had severe injuries with displacement or comminution of the head of the radius, synostosis developed in 2 with loss of rotation, and 1 recovered complete function. The remaining 6, with slight trauma, recovered complete function.

[ED. NOTE.—This article gives an excellent discussion of the subject. Operative treatment is less frequently indicated for children than for adults. If operation is to be done, it must be done early.]

End-Results of Carpal Scaphoid Fractures.—One hundred and seven cases of fracture of the carpal scaphoid were reported from the surgical dispensary of the Episcopal Hospital in Philadelphia by Snodgrass.[37] Ninety-five of the patients were males and 12 were females. The end-results were determined in 61 cases, in 48 of which roentgenographic studies were made. In 40 cases the final result was listed as good,

35. Ober, F. R.: J. Bone & Joint Surg. **14**:640, 1932.
36. Bohrer, J. V.: Ann. Surg. **97**:204, 1933.
37. Snodgrass, L. E.: Ann. Surg. **97**:209, 1933.

in 10 moderately good and in 11 poor. Five of the 61 patients had been operated on, with poor results in 3 and good results in 2.

[Ed. Note.—A more complete analysis of these cases would be of interest. From this series of cases the conservative type of treatment is shown to be the best.]

Late Results of Separation of Epiphyses.—Ireland [38] examined 18 patients with 19 epiphyseal separations, from seventy-four days to seven and one-half years after the original injury. Sixteen of these lesions were due to trauma and 3 to scurvy. Eleven patients were treated conservatively by closed reduction. Of these, 1 had shortening and 1 had lengthening as measured in roentgenograms; 2 had osseous union of the epiphysis to the shaft; 1 had deformity, and 1 had poor function, but none had arthritis. Two patients with 3 epiphyseal separations due to scurvy were treated by simple rest in bed without splints, but were given antiscorbutic food and medication. One had shortening and deformity, but in neither was there osseous union of the epiphysis to the shaft, impaired function or arthritis. Five patients were treated by open operation. All of these had subsequent shortening as measured by roentgenograms, and 4 showed shortening by external measurements; 1 had osseous union of the epiphysis to the shaft, and 1 had a resulting deformity, poor function and arthritis after removal of the epiphysis.

Osteosynthesis for Fracture of the Femoral Neck According to Sven Johannson.—Krauss [39] considered Johannson's modification of Smith-Petersen's [40] procedure of nailing the fractured femoral neck a distinct advance. Johannson inserted a Kirschner wire through the site of fracture. The position of the wire was then checked by roentgenograms, the table being specially fitted for this purpose. After the Kirschner wire had been satisfactorily placed, a special nail with a hole in its longitudinal axis was threaded on the wire and driven into the femoral neck over the guide wire. The Kirschner wire was then withdrawn. This procedure obviated the necessity for a long incision.

[Ed. Note.—This is an ingenious improvement in technic which may later prove to be useful. There is always the danger that the fracture may appear to be satisfactorily reduced in anteroposterior roentgenograms while roentgenograms in the lateral plane will show that the fracture is not reduced.]

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38. Ireland, J.: Ann. Surg. **97**:189, 1933.

39. Krauss, F.: Zentralbl. f. Chir. **60**:864, 1933.

40. Smith-Petersen, M. N.; Cave, E. F., and Vangorder, G. W.: Intracapsular Fractures of the Neck of the Femur: Treatment by Internal Fixation, Arch. Surg. **23**:715 (Nov.) 1931.

Slipping of Epiphysis of the Head of the Femur.—That some cases of slipped upper femoral epiphysis in the adolescent were due to renal rickets was the opinion of Brailsford,[41] who concluded that this condition could be diagnosed roentgenographically by an increase of the density of the metaphyseal periphery of the epiphysis, some increase in the breadth of the metaphysis, and a "woolliness" of the extremity of the diaphysis. The urine of such patients contained albumin. Under suitable treatment, consolidation took place within a month.

Results in Treatment of Fractures of the Thigh.—Brandt[42] reviewed 440 fractures of the thigh observed in Magnus' clinic in Bochum between 1925 and 1929. Seven of the patients died, 2 from hemorrhage, and 5 from embolic complications from two to seventeen days after the injury. Compound fractures were observed in 46 cases, or 10.2 per cent. They were divided into three groups anatomically: (1) fractures proximal to the trochanters, 110; (2) fractures of the femoral diaphysis, 299; (3) supracondylar and condylar fractures, 31. Treatment consisted usually of extension with the hip in midabduction and with slight flexion of the hip and knee. Skeletal traction on the head of the tibia was carried out in 369 cases, with infection resulting at the site of traction only once. No subsequent instability was observed in the knee joint. Extension was continued until consolidation of the fracture had occurred. Open reduction was attempted rarely. Nailing was done in articular fractures of the condyles. When it was necessary, position was maintained by wire traction about the fragments. This wire was removed in from three to four weeks. Light extension was the usual treatment in fractures of the femoral neck; 73.5 per cent of the cases healed without shortening. (Tables showing the end-results were not given.)

Fractures of the Spinous Process.—Bofinger[43] collected reports of 16 cases of fracture of the spinous processes of the cervical and dorsal vertebrae. In most instances the patient remained at work, and later when a physician was consulted the correct diagnosis was rarely made. The clinical signs were tenderness and pain in the lower cervical or upper dorsal region with occasional localized swelling. Lateral roentgenograms rarely showed fractures of the spinous processes, but anteroposterior roentgenograms showed irregularities and displacements instead of the normal round or oval shadows of the spinous processes. The author believed that the fracture was due to muscular pull. Local muscular fatigue seemed to be the chief predisposing cause.

41. Brailsford, J. F.: Lancet **1:**16, 1933.
42. Brandt, K. D.: Ztschr. f. Chir. **239:**294, 1933.
43. Bofinger: München. med. Wchnschr. **80:**146 (Jan. 27) 1933.

Treatment and Evaluation of Vertebral Fractures.—Schleipen [44] reviewed 109 cases of vertebral fracture observed at Freiburg in the past ten years. Extension was applied in fractures of the cervical spine. In the remaining cases the patient was kept on a hard bed until healing had occurred. Massage was begun in the second week. Sitting with support was permitted in four weeks. Standing was permitted in from seven to nine weeks. Ossification to neighboring vertebrae and arthritis of the vertebral joints were commonly seen in the region of the fracture. The mortality was 35 per cent in cervical fractures; 17 per cent in thoracic fractures, and 3.6 per cent in lumbar fractures. Death was usually due to injury to the spinal cord. Two deaths were due to fat emboli. Only 10 patients were completely without pain after two years. Normal spinal motion was found in only 23. The best results were observed in the cases in which motion was resumed early without atrophy of the spinal muscles.

[ED. NOTE.—The bibliography of the author showed that he was familiar with the methods used in America for decompression; but apparently they were not used in this clinic. One has only to read the results reported in this article to appreciate the value of modern methods which bring about the reduction and fixation of such vertebral fractures.]

RESEARCH

Healing of Bone and Cartilage After Sympathectomy.—Key and Moore,[45] using cats, produced fractures in the bones of the extremities and defects in the articular cartilage. Approximately one or two months later sympathectomies were performed, and while dilatation of the blood vessels was produced, there was no demonstrable effect on the rate of healing of the fractures or repair of the cartilage as compared to similar injuries in control animals.

Influencing Growth and Regeneration of the Bone.—Boeminghaus [46] studied the effect of the local and systemic applications of various substances on regeneration and growth of the bone in young dogs. He found that regeneration of the bone could not be influenced appreciably by intensive feeding of vitamins and calcium-rich food substances, by local hyperemia, by local injections of solutions of isotonic potassium or calcium chloride or through the use of anterior pituitary extract, provided the animals were in good health. The author concluded that in the organism that was not diseased osseous regeneration and growth proceeded at an optimum without local or systemic stimulation.

44. Schleipen, C.: Deutsche Ztschr. f. Chir. **238**:618, 1933.
45. Key, J. A., and Moore, R. M.: Healing of Fractures, of Defects in Bone and of Defects in Cartilage After Sympathectomy, Arch. Surg. **26**:272 (Feb.) 1933.
46. Boeminghaus, H.: Deutsche Ztschr. f. Chir. **238**:684, 1933.

Effect of Viosterol on the Periosteum in Experimental Fractures.— Grauer [47] found that viosterol in therapeutic doses caused stimulation of the osteogenic layer of the periosteum in experimental fractures in the guinea-pig, while overdosage produced a condition simulating osteitis fibrosa with retardation in repair and decalcification of the bone.

The Effect of a Diet Low in Calcium on the Breaking Strength of Healing Fractures.—McKeown and co-workers [48] found that a diet low in calcium had little effect on the normal breaking strength of unfractured fibulae or of healing fractures in albino rats. They attributed this to an increase in the organic elements of the bone, substituting increased pliability for a decrease in the calcium content of the bone. They concluded that phosphorus was of more importance to the strength of healing fractures than calcium.

Experimental Studies on Tuberculosis of the Bone.—Mandelstamm,[49] in experimentally produced tuberculosis of the bones, found tubercles always about the larger blood vessels whether infection was produced by intracardial injection, subcutaneous injection or intra-articular injection. The epiphyses showed a much greater tendency to the disease than the diaphyses. There seemed to be a local difference in the resistance of the tissue in various parts of a bone. Tubercles did not develop with equal frequency in different parts of the bone. There was no caseation in the bone marrow of the diaphysis, while this was frequently observed in the epiphyses. In the fatty marrow no tubercles developed. In rabbits intraperitoneal injections (lymphatic absorption) of bovine tubercle bacilli produced a generalized infection and death in about two months with numerous tuberculous foci in the bones and joints.

47. Grauer, R. C.: The Effect of Viosterol on the Periosteum in Experimental Fractures, Arch. Surg. **25**:1035 (Dec.) 1932.

48. McKeown, R. K.; Harvey, S. C., and Lumsden, R. W.: Breaking Strength of Healing Fractured Fibulae of Rats: Observations on Low Calcium Diet, Arch. Surg. **25**:1011 (Dec.) 1932.

49. Mandelstamm, M.: Beitr. z. klin. d. Tuberk. **82**:98, 1933.

CONGENITAL CLEFTS OF THE FACE AND JAWS

A SURVEY OF THREE HUNDRED AND FIFTY CASES IN WHICH OPERATION WAS PERFORMED

HARRY P. RITCHIE, M.D.

ST. PAUL

The charts and records of 350 cases of harelip and cleft palate have been reviewed. These cases were selected because, with the exception of 4 which were added to make an even number, the data are recorded by the classification and plan (figs. 1 and 2) suggested a number of years ago by Dr. John Staige Davis and myself.

This classification is based on a series of congenital clefts which involve the face and jaw. The condition of the alveolar process, i. e., whether it is normal or cleft, is emphasized to the point that it is the deciding factor in· describing the cases. Three main groups naturally follow: Group I, prealveolar cleft; Group II, postalveolar cleft, and Group III, alveolar cleft. Thus new terms of description are evolved to designate the case as a whole.

The objection to such a plan is concisely stated in the comment of a great medical editor, to wit: "Special terms in special fields tend toward confusion and misunderstanding to the general reader, and should be erased in favor of terms of common usage." This is a most valid objection. However, the common terms of harelip and cleft palate are so general in their meaning as to the conditions present in a given case, and although adjectives—single, double, complete and incomplete—are added, the effort to be more specific in description appears to have some merit. I hope that the worth of the plan may be demonstrated throughout the survey. The charts contain accumulated data on several phases of the problem of harelip and cleft palate. In order to abstract them as clearly as possible, the report is divided into four parts:

I. Familial Incidence and Associated Deformities and Conditions
II. Combination and Degree of the Clefts; Age for and Sequence of Repair
III. Operative Result and Technic Used
IV. Conclusions

1. FAMILIAL INCIDENCE AND ASSOCIATED DEFORMITIES AND CONDITIONS

One of the most interesting problems in the field of harelip and cleft palate is that of etiology. On the obverse side of the chart used is the social history, divided to be specific, of the father, the mother

CONGENITAL CLEFT LIP AND PALATE

HISTORY

General No........ .... Date... Surgical No.............

Name.................................. ....

Address.. Date of birth.........................

Sex .... Color..

FATHER. Name.................. ....

Age........................... Nationality.............................. ....

Occupation..

Habits............ ....

Mentality...

Health at time of impregnation...

Wassermann..

MOTHER. Age......................... Nationality..................................... ......

Occupation..

Habits............................. ....

Mentality...

Health at time of conception...

and for 2½ months thereafter..

Excessive vomiting............. ....

Injury during first 2½ months of pregnancy.........................

Maternal impressions...

Time of occurrence...

Wassermann..

CHILD. Legitimate..............................or illegitimate......................

Whether first child...

Other congenital clefts in the family?..................................

Relationship.................................... Location.......................

Extent...

Birth. Normal....................................... Complicated.......................

General condition..

Preliminary care..

Wassermann..

PHYSICAL EXAMINATION.

Head........................... Teeth...

Tonsils......................... Adenoids..

Chest..

Abdomen..

Extremities..

Other congenital deformities..

LABORATORY EXAMINATIONS.

BLOOD. Hemoglobin............................. Clotting time...........................

URINE. Acetone................................... Diacetic acid.........................

Albumin.................................. Sugar.....................................

SPECIAL EXAMINATIONS.

Fig. 1.—Obverse side of the chart reduced from the hospital size of 11 by 8 inches. The data are discussed in the text, with the observations that two items only are of importance, viz., familial incidence and associated deformities. However, the plan of separate notes for the parents and the child offers an orderly, concise and comprehensive questionnaire on social history.

Lip Column

SPECIAL EXAMINATION

Process and
Palate Column

Right

GROUP I. PRE-ALVEOLAR (Process) **CLEFT. (Lip cleft. Process normal).**

1. Unilateral. Right {Complete (Cleft extends into nostril) ....
   Incomplete (Does not extend into nostril) ....
   Left {Complete ....
   Incomplete ....

Draw in Degree

2. Median (rare)   Complete................................   Incomplete.................................

Right   Left 3. Bilateral. Right {Complete.......... ... .   Left {Complete ....
   Incomplete............ ....   Incomplete........................

Describe nostrils ....

NOTE: If associated with palate cleft, also fill in GROUP II form.

Draw in Degree

GROUP II. POST-ALVEOLAR (Process) **CLEFT. (Palate cleft. Process normal).**   Right   Left

1 Soft Palate.......... ....   Extent in thirds................ .. ..

2. Hard Palate........ .. ..   Extent in thirds...

Situation and attachment of septum...

Measurement of widest portion of cleft ....

Palatine arch...... ... .   High............................. Low............ ....

NOTE. If associated with lip cleft, fill in GROUP I form.

Draw in Degree

Right

GROUP III. ALVEOLAR (Process) **CLEFT. (Follows incisor sutures).**   Right

1. Unilateral.

PROCESS.   Right {Complete (Cleft extends through alveolar process) ....
   Incomplete (Cleft does not extend entirely through process) ....
   Left {Complete ....
   Incomplete ....

PALATE. Unilateral..........................   Bilateral...........................   Median...................

Complete ....   Incomplete........ ....

Palatine arch ....   High.............................   Low.............................

LIP. Unilateral...................   Bilateral ....   Median.....................

Complete.......... ....   Incomplete...

Draw in Degree

2. Median (rare). Complete...................................   Incomplete....................................

Left

Measure Process Cleft
Measure Palate Cleft
Draw in Degree

Right   Left 3. Bilateral.   Right   Left

PROCESS. Right {Complete........................ .....   Left ¦Complete
   ¦¦ .... ..

PALATE. Right ¦ ¦   Left ¦¦¦

Palatine arch.........................   High......... ....   Low.................

LIP.   Right {Complete ....   Left ¦Complete.......................
   Incomplete.......................   ¦Incomplete.........................

Locate any rudimentary structure..

Note projection of premaxilla...

Note rotation of premaxilla.. . ...

Situation and attachment of nasal septum..

Measurement of cleft at alveolar process..

Measurement of widest portion of palate cleft...

Measure Process Clefts
Measure Palate Clefts
Draw in Degree

....

If previous operations performed elsewhere, give dates.

Fill in original condition on proper group form.

Impression........................

Recommendation...... ....

Photographs. Date...   No.................................

Date..   No.................................

X-ray plates. Date.........................   No.................................

Date.........................   No.................................

Palate casts. Date..............................   No.................................

Phonographic speech records.

Date.......................   No.................................

Date......................   No.................................

Fig. 2.—The reduced reverse side of the chart, with plans for graphic, literal record of the case as a whole. In Group I diagrams appear in the lip column only, so that no case with a cleft of the alveolar process and hard and soft palates can be placed in this group. In Group II there are no diagrams in the lip column. There is a normal alveolar process on the diagram in the palate column. In Group III there are diagrams in both lip and palate columns, because in this group all clefts appear except in cases in which there were normal hard and soft palates, in which instance the outlines pertaining to the lip and process are marked and the outline pertaining to the palate is crossed out.

and the child (fig. 1), which is recorded in the effort to collect data which may bear on the question of cause.

Neither the ages of the parents nor the disparity of ages between the father and the mother apparently have any bearing on the problem. A record was made of nationalities and consequent cross-breeds. It is interesting to note the many strains that go to make up the American citizen, but I cannot interpret these as having a bearing on the subject.

TABLE 1.—*Records of Cases with Familial Incidence*

Case	Patient	Group	Member of Family Affected
1	L. A.	III B.	Mother, cleft lip
2	K. F.	II-2/3	Father, identical cleft
3	R. S.	III L.C.	Uncle, cleft lip
4	L. H.	III L.C.	Brother, cleft lip, right
5	R. S.	III B.	Brother, cleft lip, right
6	E. H.	III L.C.	Maternal uncle, cleft lip
7	W. F.	III B.	Cousin, both lip and palate clefts
8	J. D. N.	III B.	Paternal great uncle, cleft unknown
9	D. K.	III L.C.	Sister, complete cleft lip and palate, left
10	D. A.	III, with normal palate	Father, cleft lip and palate
11	F. J.	III L.C.	Sister, identical cleft
12	S. H.	II-2/3	Maternal grandmother, cleft palate
13	A. H.	II-2/3	Sister, cleft palate
14	T. H.	II-2/3	Sister, cleft palate
15	S. H.	II, soft palate only	Father, complete cleft
16	J. W.	III L.C.	Is a twin: sister normal
17	G. H.	III, with normal palate	One brother and one sister-with clefts; no record of form
18	A. R.	III L.C.	Brother, Group III
19	L. N.	III R.C.	Mother, III L.C.
20	L. B.	III R.C.	Cousin of father; no form recorded
21	G. D.	III L.C.	Cousin of father: no form recorded
22	A. F.	III L.C.	Paternal aunt; no form recorded
23	J. R.	I L.	Maternal uncle; no form recorded
24	F. R.	III B.	Two brothers, each in Group I
25	H. K.	II-2/3	Cousin, Group II
26	R. T.	III R.C.	Cousin on maternal side, Group III
27	C. G.	III B.	Father, Group I R.
28	H. H.	III L.C.	Aunt, III B.
29	M. T.	III L., with normal palate	One brother, III B.
30	G. S.	III B.	Three brothers: Peter, I R.; Mike, III L.C.; Ed, I L.
31	R. P.	III L.C.	One brother, Group III
32	J. C.	III B.	One brother, III L.C.; father's cousin, lip and palate clefts
33	A. D.	III B.	One brother, Group II
34	E. C.	I R.	Twin; sister normal

A study of the mentality of the father and the mother was also made. This interpretation is most elusive, and while it is not uncommon to encounter mothers or fathers who are exacting and suspicious, and some that may be loosely described as morons, on the other hand there are many of a high degree of intelligence. There was only 1 case in which there was a history of gross mental disorder.

Wassermann tests were not done as a routine measure, but were made occasionally when syphilis was suspected. There is a record of only 1 case of syphilis, and that was in the mother. The history of the mother showed some evidence that nausea and vomiting were present in the early months of pregnancy.

Questions as to maternal impressions so infrequently evoked a positive response that the few cases cited can have no value. In fact, most parents had never heard of the condition.

The first item of possible value in the study of etiology is the familial incidence, concerning which there are several interesting stories. The cases in which there was a familial incidence are presented in detail in table 1. The groups are described in the tables in the text as follows: III B., Group III, bilateral; II–2/3, Group II, two thirds of hard palate affected; III L. C., Group III, left complete, etc.

In the series of 350 cases, there were 34, or 9.2 per cent, with a history of familial incidence. When one remembers that few families

Fig. 3.—A set of twins; the boy is normal, and the girl has all the clefts on one side.

are acquainted with their history, other than that of members with whom they are in immediate contact, the percentage may be really large.

In case 30, the child had a double harelip and palate and was the fourth child in sequence with a cleft. I repaired the cleft of the three brothers. This is the only case of this kind in the series.

In the two sets of twins, in both cases apparently not identical, one child had a cleft (fig. 3) and the other child was normal. In another set, one child had a double harelip and the other one was normal, while in a pair of true identical twins (not in this series) both had the same series of clefts, but reversed.

Two sisters with Group II clefts had palates apparently from the same mold.

A father, 40 years of age, had a Group II cleft which had never been repaired, and when his daughter was seen it was quite startling to find that they had identical clefts.

In 26 of the cases there were associated deformities and other conditions (table 2). The 8 with hernia are not of great significance. Examination for thymus was not made as a routine; in fact, it was made quite infrequently after negative roentgenograms had been obtained several times. The unexplained death reported in the mortality statistics may well have been caused by the presence of an enlarged thymus. The case of multiple clefts of the face and jaw (fig. 4) in my

TABLE 2.—*Cases with Associated Deformities and Other Conditions*

Case	Patient	Group	Associated Deformity and Conditions
1	Y. C.	III B., with no mesial segments in the process	Umbilical hernia
2	N. S.	I R.	Large birth mark on left hand
3	R. L.	III L.C.	Right inguinal hernia
4	F. C.	III B.	Mongolian
5	T. C.	II-1/3	Mentally defective; hydrocephalic (Spears)
6	R. D.	III L.C.	Subnormal with big head
7	J. H.	III L.C.	Left hydrocele
8	J. T.	III R.C.	Congenital deformity of right hand
9	D. G.	III R.C.	Cleft at each angle of mouth; coloboma of eyelid; dermoid of eyeball; subnormal
10	D. P.	III L.C.	Subnormal
11	L. H.	III B.	Subnormal
12	R. N.	II	Mongolian
13	J. W.	III R.C.	Indirect inguinal hernia
14	K. C.	III L.C.	Right inguinal hernia
15	B. S.	II-1/3	Umbilical hernia
16	H. D.	III B.	Extra thumb on right hand
17	G. K.	III B.	Equinovalgus; absence of left thumb
18	E. J.	I L.	Enlarged thymus
19	W. S.	III R.C.	Right inguinal hernia
20	R. J.	III R.C.	Mentally subnormal
21	L. O.	II-2/3	Enlarged thymus
22	H. B.	III R., with normal palate	Penile hypospadias; brother with spina bifida
23	M. B.	I L.	Eczema and enlarged thymus
24	B. N.	III B.	Undescended testicle
25	C. K.	II-2/3 soft	Umbilical and right inguinal hernia
26	L. W.	III R.C.	Umbilical hernia

series is one which, along with the reports of others collected from the literature, indicates the many possibilities of failure in embryonal growth and supports the statement that harelip and cleft palate are only a part of a group of congenital deformities in this area.

The phase of the problem of congenital clefts of the face and jaw which has a moral tinge is the question of operation on the mentally defective. There were 2 mongolians in my series. The mongolian child is usually active and vigorous physically, and it appears proper to repair the clefts of such a child. The more severe cases of mental defect present a great problem. There were 3 children who showed severe mental defect, but in each instance I was greatly influenced by the desire of the sorrowing parents, and the clefts were repaired. The various other deformities and conditions are reported as a matter of record.

The 34 cases with familial incidence and the 26 cases with associated deformities and conditions total 60, or 17.1 per cent of the total number of cases.

I have no particular comment to make. The survey of this part of the subject is offered in the hope that the reader may find some points of interest bearing on this phase of the problem of harelip and cleft palate.

II. COMBINATION AND DEGREE OF THE CLEFTS; AGE FOR AND SEQUENCE OF OPERATION

This part of the survey deals with the case as a whole, the data bearing on this phase of the subject being recorded on the reverse side of the chart (fig. 2). The diagrams on the chart are illustrated in the text by typical cases. The groups are studied separately.

Fig. 4.—A child with multiple clefts of the face and jaw. The cleft in the body of the lip is due to failure of the right maxillary division to unite with the frontonasal division. The clefts at the right and left angles of the mouth are due to the failure of the right and left mandibular divisions to unite with the right and left maxillary divisions, so that three breaks appear in the encircling musculature of the mouth. The muscle elements of the right maxillary division are out of contact on both sides and appear as a rounded, humped-up ball of contractile tissue. The several clefts were repaired on the same principle of muscle repair, which apparently fits the cleft at the angles as well as that in the body of the lip.

Group 1. Prealveolar Process Cleft (fig. 5).—In this group, the alveolar process and the hard and soft palates are normal. The defect is that of a cleft in front of a normal alveolar process. The statistics on this combination are as follows:

	Cases	F.	M.
Right cleft (fig. 5 A)	11	9	2
Left cleft (fig. 5 B)	26	10	16
Bilateral cleft (fig. 5 C)	1	1	0
Total	38	20	18

The degree of the cleft may vary from simple notches at the vermilion border and lines on the skin, etc., to more severe clefts, but in none of the cases has the floor of the nostril been involved. These are the incomplete harelips. I have yet to see a complete harelip without a cleft of the alveolar process. In all of the cases there was some muscle contact in the lip, although this feature may be slight. The nostrils are usually well alined, yet it is possible to have a case in which the ala is pulled aside.

The age for operation in group I is within the judgment of the operator and depends on the circumstance of convenience, health of the child, etc. There is no hurry from the surgical standpoint because the tissues of the lip develop along with the body (fig. 9). The babies nurse normally, and the operation in many cases is postponed until they
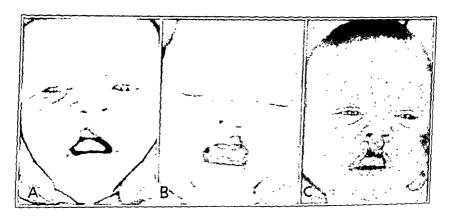
Fig. 5.—Group I, prealveolar cleft: *A*, right; *B*, left; *C*, bilateral.

are weaned. It is just as wise to perform the operation early and then put the child back on the breast. It is a fair statement to say that the operation may be performed any time after feeding is established and the baby is gaining weight.

Group II. Postalveolar Process Cleft (fig. 6).—In this group the lip and the alveolar process are normally united. The hard and the soft palate are cleft in varying degrees. There is one definite, constant similarity; the clefts are always symmetrical. They differ in the anterior posterior extent and in the width measured at the junction of the hard and the soft palate. There is equal tissue on either side, except in an occasional case in which I have noted an apparent disparity in the soft palate. It is apparent and not real, because in the denudation and suture it is possible to make an even approximation.

It is not easy to illustrate the various degrees of clefts, so a photograph of an 8 year old boy with a II–2/3 combination is shown, supplemented by a copy of the diagram from the chart (fig. 6).

The statistics in this group are as follows, it being understood, of course, that whenever the hard palate is involved, the soft palate is completely cleft:

Degree of Cleft		Cases	F.	M.
Hard palate.............	3/3	11	7	4
	2/3	22	17	5
	1/3	6	5	12
Soft palate only...........		6	4	2
Total		56	33	23

In Group II the question of the use of direct force to assist in closing the cleft has never been raised elsewhere nor used in any case in this series, because it is my observation that no matter what the degree of the cleft may be, the occlusion of the upper and lower jaw is normal. Any surgical attempt to narrow the cleft is impossible. In all but 6
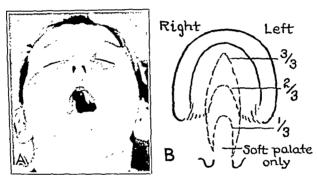
Fig. 6.—Group II, postalveolar cleft. Illustration of this type of the defect is limited to *A*, as it is difficult to photograph the various degrees which are indicated on the diagram.

cases the presence of a cleft hard palate has evolved a situation which raises the question of the sequence of repair of the hard and of the soft palate.

The II–3/3 Palate: The repair of a II–3/3 palate is one of the greatest problems in this field. Fortunately, in my series there were only 11 cases with a defect of this degree. The septum and vomer are exposed their whole length. The condition looks like a double cleft palate, but it is simply a medial cleft which has extended to the anterior palatine foramen, as far as the cleft may go without involving the alveolar process, in which case it would be recorded under Group III.

Operation on such a combination has never been attempted in this series before the child is 2 years old. In several cases the operation has been postponed until the child is 3 or 4 years of age. The tissues grow with the body, and during this period there is some normal adjustment and development of resistance to handling.

At this point it seems fitting to discuss the problem of the sequence of operation on the hard and soft palates with the understanding that the statements apply not only to the II–3/3 palate but to the other combinations as well, that is, the palates in Groups II and III.

The sequence of operation on the hard and soft palates may be solved by several plans.

1. An attempt may be made to suture both the hard and the soft palate at one sitting.

2. The hard palate may be sutured, and the soft palate left for later repair.

3. The soft palate may be sutured, and the hard palate left for later repair.

4. The soft palate may be sewn and the hard palate raised and packed for several days, when the packing is removed and a delayed suture of the mucoperiosteal flaps is made.

Plan 1 has not yielded a primary result in the cases of the II–3/3 palate. In 1 case the right mucoperiosteal flap sloughed out, and although this healed so that the closest inspection was required to see the loss, this plan appears to me to exceed the possibilities of the tissues and should be put aside in favor of other steps of sequence.

Plan 2 is satisfactory because the hard palate will always heal, even in the presence of infection. If infection should occur, the fact that the soft palate is unrepaired affords wide avenues of drainage. This plan has not been used for postalveolar process clefts, although it has become popular with me in the repair of the palate in the Group III case, for it appears to offer the best chance of solving that problem.

In plan 3 the soft palate is sutured, and the hard palate is left for later repair. The effect of such a procedure is the same as that obtained with plan 1 when the suture line of the hard palate fails to hold. In the repair of the soft palate it is always necessary to mobilize the hard palate, the handling of which results in an inflammation which is residual over long periods, and unless the secondary suture is undertaken within ten days or two weeks, it seems wise to postpone it for six months or more. The high percentage of success in secondary repair of the hard palate may support this plan, but it has purposely not been followed in any case in this group.

Plan 4 has been done several times, and the ratio of success to failure of 2:1 (see part III) is illustrated by my experience in 3 patients who were under my care at the same time. In 2 cases there was apparently a perfect result, while in the other the child had a high temperature and was prostrated, so that any immediate secondary repair was precluded and the procedure resolved itself into plan 3. An objection to this plan is that a second anesthetic given within a period of from seven to ten days following a rather elaborate procedure carries a risk which must be carefully considered in the individual case.

As previously stated, the Group II–3/3 combination presents one of the greatest problems in this field of surgery, and whenever a primary result is attained I consider it a great victory.

In my experience the best chance of success is with plan 4.

The II-2/3 Palate: This defect is shown in figure 6, and it occurred 22 times in my series.

In this type of defect there is a good chance of obtaining a primary result with the straight Langenbeck-Warren operation of median suture, viz., plan 1. There is an occasional case which apparently merges into the combination just described, and plan 4 has been tried.

The 2–1/3 Palate: For this combination, of course, there is only one method of repair, plan 1, because it is seldom that more than two stitches, usually superficial, are required in the hard palate. But I have found that these may fail as well as a whole suture line.

The earliest age at which operation was performed in the series was 6 months, but the baby was large and strong, and the result was perfect. I still feel, however, that at such an age the risk is too great, and the operation should be postponed to the second year or later.

Soft Palate Only: There were only 6 cases in which the soft palate alone was involved. It is interesting to me to find that of the 7 cases of operative failure in cleft of the soft palate, there were 1 secondary and 2 primary failures in this simple form (part III).

An interesting condition appears in the soft palate which is not evident until the child begins to talk. A transparent median line is not found until the child develops a nasal tone in speech. The mucous membrane has healed, but the muscles are apart. I believe that a child with this defect is entitled to a formal repair in order to effect contact of the muscle bodies.

In Group II there were 56 cases in which operation was performed. This number in no way represents the real relative incidence because these patients are under observation and preparation for operation over long periods. The average age at which operation was performed varied from 14 months to 2 years.

Group III. Alveolar Process Cleft (figs. 7 and 8).—The value of the classification and plan of record is most evident in this group. In Groups I and II the combination and degree of the clefts run rather closely to form because the alveolar process is closed. When the process is cleft, as in Group III, there are so many possible combinations and degrees of failure in embryonal growth that the usual terms of description appear most inadequate.

The chart allows the description of each cleft separately, viz., the lip, alveolar process, hard palate and soft palate. Several combinations may be thus accurately described—cases which it is not possible to record clearly in any other way.

The incidence of the various combinations in this group is as follows (fig. 7):

Defect	Cases	F.	M.
III L. C.	110	33	77
III R. C.	55	17	38
III. B.	51	17	34
Total	216	67	149

216 of 350 = 61.7 per cent.

Fig. 7.—Group III, alveolar cleft: *A*, right complete; *B*, left complete; *C*, bilateral.

Fig. 8.—Group III, alveolar cleft with normal palate: *A*, right complete; *B*, left complete; *C*, bilateral.

The incidence of 61.7 per cent is the largest of any combination of the clefts. All of the clefts are present. The cases vary greatly in degree, not because of the lip or palate cleft, but on account of the process cleft. The literature revolves about this group.

The statistics on these combinations with a normal palate follow (fig. 8):

Defect	Cases	F.	M.
III L. C.	24	7	17
III R. C.	11	7	4
III B.	7	2	5
Total	42	16	26

42 of 350 = 12 per cent.
258 of 350 = 73.7 per cent.

The incidence in the subdivision of Group III appears between that of Group I and Group II. The statistics of 12 per cent is close to similar reports of the literature.

About three fourths of all cases are recorded in the third group. The operator's problems in repair of the lip and of the hard and the soft palate in this group are generally the same as in Groups I and II. But a problem appears which has so deeply impressed me that I believe it should be identified as the most important in the whole field of surgery—the cleft in the alveolar process. What shall be done for it and when? Various avenues of study indicate, if they do not prove, that the cleft in the process is a separate cleft from the others and is particularly important because it involves the most resistant of the tissues of the body—bone. The time of operation is therefore more important than with other clefts which invade soft tissue only. Soft tissue may be mobilized at any time of life, but with the bone cleft there is only one time when this cleft may be closed, and that is as early as is compatible with the condition of the child, while the bones are soft and pliable. If the baby is allowed to grow to the age of 3 months and beyond, the bones become set and fixed, and it is increasingly difficult to effect contact of the margins of the cleft. The various plans of repair used in this series, the results and the discussion of the relative value of direct force and indirect force will be found in part III.

Whatever the plan used, I repeat that the ease of accomplishment and the effect depend entirely on the softness of the bones and the width of the cleft. The cleft of the alveolar process is the first one to be considered.

The cleft of the lip is second in importance to that of the alveolar process in the consideration of the age for operation and the sequence of the steps in this group. In Group III the lip has been repaired as early as possible, not only because of the appearance and function of the lip itself, but particularly because of its effect in closing the cleft of the alveolar process underneath. Although the forms may be the same as in Group I, the lip in Group III is associated with a bone cleft of the alveolar process. Most lips are repaired before the child is 3 months of age.

The clefts of the hard and soft palates have never been repaired before the fourteenth month, as stated in the section on Group II. At this time the child is observed and operated on if the cleft at the junction of the hard and soft palate measures no more than 10 mm. Often the operation is postponed until the seventeenth month, and more recently until the child is 2 or more years of age.

Observation of the results of repair of the hard and soft palates has brought up another question, viz., the selection of the time of operation. The latitude (45 degrees) in which St. Paul is located exhibits wide

ranges of weather which influence the patient's reaction to these changes. Since the child must be hospitalized and often comes from long distances, this phase of the subject should be carefully considered. In repair of the clefts of the alveolar process and of the lips the question of selection of the time for operation is minimized because the cleft of the alveolar process should be molded and the lip repaired early. The question, however, is most important in repair of the hard and the soft palate as infections may lead to failure. These operations are often postponed in the expectation of equable weather.

The subdivision of Group III (fig. 8) that is most interesting to me is the combination of a cleft of the lip and of the alveolar process but normal hard and soft palates. These cases support the statement that the alveolar process cleft is not a part of the palate, but is formed in relation to the lip.

This combination occurred in 42 cases. Figure 8 *A* shows this condition excellently. In figure 8 *B* it is not so evident. In figure 8 *C* is illustrated a problem which is almost as great as that presented by the II–3/3 palate. In this case the large premaxilla apparently has no place between the two lateral divisions which appear close together.

The law of early repair of the alveolar process also holds in this combination. The premaxilla must be pushed down as early as possible. The question of the use of direct force through wires has never been raised in this combination. There is a tendency to delay replacement of the premaxilla because the palate is normal, and apparently there is nothing to repair but the lip. Yet in this combination there are more unsatisfactory nostrils than in any other, owing to the fact that an attempt to close the alveolar process cleft is postponed until the lip is repaired.

The photographs of the six cases in Group III (figs. 7 and 8) merely represent typical cases. Added to these are many of different degrees. An exact record of the original condition is necessary to appraise the results of late repair properly and to evaluate the surgical principles of repair. The classification and plan of record appear to meet the requirements.

By reason of the great variety of combinations and degrees, rules of procedure can be only generalized as follows:

1. Repair of the alveolar process cleft should be done first as early as is compatible with the condition of the child.

2. Repair of the lip is left to the judgment of the operator. The age for operation depends on the degree of the cleft of the alveolar process.

3. Repair of the hard and the soft palate in Groups II and III should be postponed to the second year or later, with particular attention to the

season selected for operation. The sequence of operation in the wide clefts should be considered. I have a preference for suture of the palate first and later repair of the soft palate.

III. OPERATIVE RESULTS AND TECHNIC USED

The 350 children were subjected to 567 operations; that is, some procedure or combination of procedures was performed which required an anesthetic. The disparity between the total number of cases (350) and of operations (567) is explained in part by the fact that during a long period of trial and error, different sequences of steps were used; the hard palate was repaired and the soft palate left, or the steps were reversed; or the alveolar process was wired and the lip repaired at a second sitting, etc.

The mortality has been 1.4 per cent of the total number of patients (350)—less than 1 per cent of operations (567). Two patients died of pneumonia: One, a child in whom the whole palate was repaired, died on the twenty-first day, although the stitches held; the other child died on the sixth day following repair of the lip. One patient, 6 weeks old, died of erysipelas, which developed in an abrasion of the left cheek, and although the stitches held in a bilateral cleft of the lip, death occurred on the tenth day. A patient subjected to repair of a unilateral cleft died the afternoon of the operation from suffocation due to inspired vomitus, as proved by autopsy. The fifth patient died on the operating table from an undetermined cause other than shock.

When one considers that the babies and children in this series were operated on at several different hospitals, with a changing group of anesthetists, and that as a class the patients are delicate, the record appears favorable. It is due in part to the fact that no operation was undertaken without the permission of a pediatrician, and again to the rule that when bleeding occurs during one stage of the operation, it shall be completely controlled before another stage is undertaken. So often postoperative concern is due not to the length of operative time or to the quantity of anesthetic, but to the loss of blood.

In the study of operative results the plan of the classification has been followed wherein the whole palate is resolved into its component clefts. The lip, alveolar process and hard and soft palates have been studied separately to determine, if possible, wherein lies the greatest chance of failure or of success. Most of the children have received my personal attention, except those at University Hospital, where I have had the assistance of my associates, Dr. Carl Waldron, Dr. W. T. Peyton, Dr. Logan Leven and others who from time to time have been interested. But since in all cases I have assumed some measure of responsibility, it seems fair to include them.

Cleft Lip.—At first I intended to separate the incomplete and complete forms of cleft lip, but so many of the so-called incomplete forms, whether in Group I or III, were found to be complete as regards muscle contact and to present the same problems of repair that they are discussed together here irrespective of the degree of the cleft. In the repair of this defect I have used my interpretation of the Mirault operation, the Rose operation, the Nelaton flaps, the modified Hagedorn and Thompson calipers, etc., but the large majority of clefts have been repaired on a principle suggested some years ago and called "a muscle theory repair of the lip." The theory was based on the observation that the general scheme of formation of all lips was the same in all persons, but with infinite variety of detail in the disposition, control

Fig. 9.—Photograph illustrating the muscle theory repair of the lip. The same picture may be obtained in the infant by electrical stimulation, not only before operation, but after suture.

and development of the tissues. The theory is simply illustrated in figure 9, the photograph of a boy of 8 years who grew to this age with his lip out of contact. It is to be observed that the active tissues of the lip develop along with the body, and that physiologic action is under the control of the person at all times and under all circumstances (fig. 9 *A*). The most direct plan for repair appears to be to suture the lip on lines of denudation determined by the active elements of the lip in the hope that if the parts are united at the peak of their physiologic action such effort will yield the best chance of anatomic replacement normal for that child. In the infant, when stimulated by the battery before operation, the same picture as illustrated in figure 9 is obtained. On every possible occasion I have stated and reiterated that this theory presented no new operation, but was simply an effort to determine a common principle of repair which would fit anatomic and physiologic require-

ments, no matter what the combination and degree of the cleft in the lip might be. The anatomic basis has been challenged because it may be safely said that no two lips are exactly alike. I have tried to dissect the orbicularis oris in the infant cadaver, and it cannot be done. Whatever may be the anatomic picture in a given case, there is always present the physiologic action which produces the pucker of the lips. The symmetrical pucker depends on the normal direction of the muscle bundles and, if the effort is made to maintain these relations without distortion, the infant presumably has a better chance to develop its proper facial expression. The theory appears to have a logical conclusion, but, of course, can be supported only by clinical evidence.

The statistics on the lip are as follows:

$$
\text{No. of cases on which operation was done} \quad \begin{cases} \text{Left} & 160 \\ \text{Right} & 77 \\ \text{Bilateral} & 59 \end{cases} \quad 296, \text{ or } 84.5\% \text{ of total (350)}
$$

$$
\text{No. of failures} \quad \begin{cases} \text{Complete} & 3 \\ \text{Partial} & 4 \end{cases} 7 \\ \begin{cases} \text{Flat and flaring nostril} & 28 \\ \text{Narrow nostril} & 4 \\ \text{Kinky nostril} & 4 \\ \text{Vermilion border notch} & 4 \end{cases} 47, \text{ or } 15.9\% \text{ of } 296 \text{ cases}
$$

In 47 cases, or 17 per cent, I made a note to show that I was dissatisfied with the result. I feel sure that this percentage would be largely increased by the legitimate criticism of colleagues, and voluntarily increased in the late appraisal of the cases.

There was complete failure in 3 cases: A bilateral cleft lip separated with loss of tissues in the prolabium—a horrible deformity, one of the great tragedies in this field. One unilateral cleft lip separated its whole length after repair without apparent infection. This is the only case in which a secondary repair was immediately attempted with a second failure of union. Figure 10 shows the result of a delayed third effort. This case supports my general idea that should failure occur, follow-up repair should be postponed until inflammatory reactions have subsided. One side of a bilateral cleft failed to hold, and follow-up closure was done (fig. 11). I do not find such experiences illustrated in the literature, and I thought that it might be interesting to show the usual picture. In the bilateral case the principal point of criticism is that the muscle elements are probably out of contact. If this is so, the lip will not grow along with the body and the chances are that a flat, immobile lip will result.

My charts contain notes on partial failures, the most frequent of which is the resulting flat and flaring nostril. The deformity of the nose is so apparent that I find myself often evaluating the result of

Fig. 10.—The photograph of the result of a third operation in the case in which the primary and secondary repair failed.
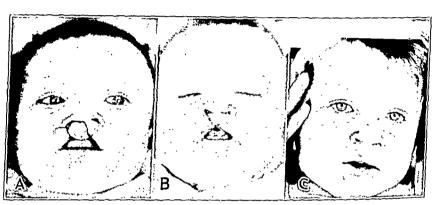
Fig. 11.—The original condition in this case is used to illustrate a Group III bilateral alveolar process cleft (fig. 7 C). Both sides of the double cleft were repaired at one sitting. The right suture line failed to hold (A) and was repaired in six months (B). The condition when the boy returned for repair of the palate is shown in C.
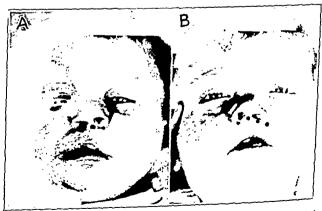
Fig. 12.—Flat and flaring nostrils following repair of a right and left complete cleft lip.

repair of a cleft lip by the condition of the nostrils. Reposition of the ala in the unilateral cleft to compare favorably with the normal has been the *bête noir* all through this work. The cause of this frequent postoperative deformity is suggested by the following study. Figure 12, which illustrates the situation, shows a right and left unilateral cleft determined by measurement with calipers and by electrical stimulation. The measurement indicates that the flat nostril is due to the fact that the floor of the reconstructed nostril is twice as wide as the normal, as shown by the dots. Stimulation reveals that there is a V-shaped piece of tissue in between the upper bundles of the active tissue which are out of contact at this point. The body of the lip, the line of the vermilion border, the eversion of the mucous membrane and the mobility of the whole structure have been obtained not as a result of any personal
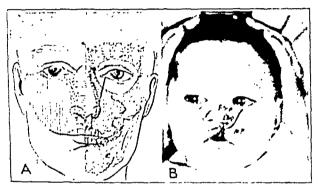
Fig. 13.—*A* is a tracing made from the diagram in the work on embryology by Fischel of Vienna. *B* shows the attempt to follow the marking of the tracing in a clinical case. *F N P* indicates frontonasal process; *L N P*, lateral nasal process; *M P*, maxillary process.

opinion of mine as to how the repair should be made, but simply on lines of denudation determined by the active elements. Thus the main lead to proper repair of the body is offered by the arrangement of tissues peculiar to the case itself. However, the nostril may or may not be in proper form, and if it is not a striking deformity results. An explanation of the double nostril must be found. Fischel of Vienna, in his text on embryology, states clearly that the complete cleft of the lip is a combination of two embryonal clefts (fig. 13 *A*). The cleft in the body of the lip involves the active elements. Its presence is due to a failure of contact of the lateral maxillary process and the infranasal process of the median embryonal division. An extension of the cleft beyond the structure of the lip does not extend into the nose but runs outside of the ala through the cheek and may reach the eye to form a coloboma. The case of multiple clefts of the face (fig. 7) indicates

the direction and possible extent of this cleft. The cleft in the floor of the nostril is a different cleft formed entirely in the median embryonal division. Its presence is due to a failure of the lateral nasal process to establish contact with the globular process. In order to follow clinically the embryonal diagram (fig. 13 *A*), markings were made on an incomplete harelip (fig. 13 *B*) to indicate that the tissue in the angle between the two clefts is probably an extension of the lateral nasal process. I have cut this reflex tissue away from the columella (fig. 14), denuded it and sewed it back on the maxillary tissues. The result was a perfect picture of a complete harelip. When the maxillary process was denuded, the muscle elements, as shown by the stimulation with the battery, were superficial and reached squarely to the margin of the cleft. When the band was sutured, the muscle ends were deeply placed. It appears to me that in both unilateral and bilateral harelips there is a reflection of the

Fig. 14.—The experimental operation described in the text undertaken to determine the embryonal origin of the reflection of the incomplete cleft lip and the position of the reflection in the complete cleft lip.

lateral nasal process onto the body of the lip. This growth is epithelial tissue only and covers the upper bundles of the active tissue of the maxillary division. The explanation of the flat and flaring nostril can now be fairly made; this tissue has been brought into the body of the lip, whereas in the complete cleft lip it should be lifted in order to denude the upper bundles of muscle for exact suture to the bundles of the other side of the cleft.

In figure 15 *A*, the diagrammatic denudations for the body of the lip are correct, but at the nostril the tissue in the grasp of the mattress stitch, without particular attention to its position, may be brought into the body of the lip instead of being turned into the nostril, as in figure 15 *B* and *C*.

The steps of the operation for unilateral cleft lip as performed are as follows:

The muscles are stimulated by the battery, and the lowest and highest points of motion are marked by ink dots. On the medial side of the cleft, two marks only are required, one at the vermilion border and one at the base of the columella,

so that denudation for exposure of the muscle elements is always in a straight line. On the lateral side of the cleft, the muscle elements are apparently bunched. Three points are determined: one at the base of the ala, one on the vermilion border and a variable point on the margin of the cleft. The denudation of the short side is always staggered. The distance between the ink mark at the base of the ala and the point on the margin of the cleft is measured by the caliper, one point of which is placed in the upper ink dot on the medial side and the other point is swung into the nostril along the epithelial reflection at the base of the columella.

The denudation of the medial side is made by connecting the upper and lower ink dots on the body of the lip by an incision at the margin of the skin and the careful dissection and removal of the mucous membrane. The skin and mucous membrane are undercut in order to make the body of the lip a separate entity. The ink dot in the nostril and the upper ink dot on the lip are connected by an incision. The epithelial reflection in the nostril is thus raised in the form of a flap to become the inner half of the floor to the nostril. On the lateral side of the cleft, the ink dot at the base of the ala is connected by an incision through the skin only, with the ink dot on the margin of the cleft. This is dissected to make a flap, which becomes the outer half of the floor of the nostril. The raising of this
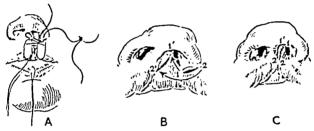
Fig. 15.—*A*, a copy of the original drawing demonstrating the repair according to the muscle theory. *B* and *C* illustrate the incision for the flap and the points of suture. It is difficult to draw this important step of lifting the flap from the muscles. The incision *1-2* connects the ink mark at the base of the ala and the ink mark on the cleft margin. The flap raised is triangular in shape with the point of the triangle at *1*. This step permits exact suture of the muscles at *2* and *2'*. The tip of the flap at *1* is sutured to the epithelial flap in the nostril at *1'*.

flap bares the upper bundles of muscle elements on the short side. The ink mark on the margin of the cleft is connected with that on the vermilion border, and the mucous membrane is dissected as on the medial side. On the body of the lip the effort is made to obtain the picture shown in figure 15 *A;* on the nostril, the picture shown in figure 15 *B*. The stitches used are the same as shown later in figure 30, but they are placed on the mucous membrane side, except at the vermilion border, where it is important to make more exact approximation of the muscle elements on account of the vermilion border of the lip and the eversion of the mucous membrane. In this lower stitch, the simple end-on stitch is used. I have always had the idea that the top stitch of the muscle *2-2'* (fig. 15 *B* and *C*) would determine the rotation and position of the ala. This idea I have found correct. The difficulty has been to find a way to make the approximation exact.

Since these steps are more fully developed, there has been a definite improvement in the results with some excellent replacements, of which figures 16 and 17 are examples.
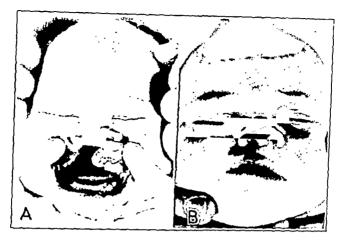
Fig. 16.—*A*, Group III unilateral cleft, right complete, showing the original condition when the mouth is stretched. *B*, the repaired lip at rest.
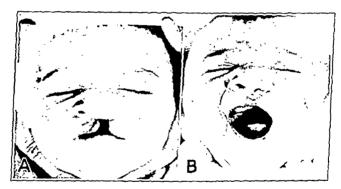
Fig. 17.—*A*, Group III unilateral cleft, left complete, with the original condition at rest. *B*, the repaired lip when stretched.
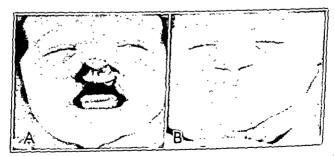
Fig. 18.—A case of double cleft lip shown to support the statement in the text that the failure of the columella to grow and the nose to project is due to the wide separation of the ala.

In the cases of the kinky nostril many things have been tried, but the rotation of the ala appears to correct this deformity as well as any method.

Bilateral Cleft Lip.—In double harelip, the nostrils may be made to look alike; at least there is seldom the gross deformity evident in the comparison of a poorly constructed and a normal nostril.

The trouble in this form of lip is in the tip of the nose and the growth of the columella. Figure 18 is shown as a probable explanation of this condition. The alae are twice as far apart as normal, and the effect is as though a rubber band had been drawn taut over the tip of the nose so that this part could grow only by separation of the cartilages. The failure of the nose to project properly has led to many suggestions for repair, the most interesting of which brings up a legitimate question as to whether the prolabium of the lip belongs to the

Fig. 19.—*A*, the combination of cleft lip in which one side is complete and the other incomplete. The follow-up picture (*B*) shows that the prolabium will develop if properly placed. Note the double nostril on the left side.

columella, to be used to add to its length, or whether it belongs to the body of the lip.

From the embryology it appears that the infranasal process of the median division extends downward to be incorporated into the vermilion border of the lip and joins the maxillary divisions on either side. Clinically, this fact is supported from several angles, but particularly in the case (fig. 19) in which there is a complete cleft on one side and an incomplete cleft on the other, with the prolabium presenting in various states of development. The temptation to do something to supplement the tissues of the prolabium is great, but to do so would bring tissue away from the normal area—if the statement that this structure is a part of the lip is correct.

The case shown in figure 19 was selected for *two reasons*: First, the suture lines are more evident than is to be desired, but the picture shows

plainly the plan of repair with normal growth of the prolabium if given a chance, and second, the double width nostril is present. The latter condition may not be a gross deformity, but in this case the right nostril has not been properly reconstructed.

In complete double harelip there is now sufficient evidence to state that there is no muscle in the prolabium. Stimulation with the battery fails to obtain action, and Mullen, in a more recent paper on the comparative anatomy of this area, brings definite support to this statement. The muscle elements formed in the maxillary divisions migrate to interdigitate between the skin and the mucous membrane of the prolabium to form a normal lip.

Thus, in all cases except a trial case here and there, the effort has been to bring the prolabium into the body of the lip and to make as direct contact as possible of the muscle elements of the lateral divisions.

Double harelip has been repaired in three ways.

Fig. 20.—*A*, the result of a modified Hagedorn operation. *B*, the result following an attempt to bring into contact the musculature of the right and left maxillary divisions between the skin and the mucous membrane of the prolabium.

Figure 20 *A* shows what is interpreted to be a modified Hagedorn operation, differing only in degree from Hagedorn's original illustrations. The mucous membrane of the prolabium has been sacrificed, and the maxillary divisions are brought in direct contact below it. Clinically, these tissues may grow well but there is a risk of a tight lip at the vermilion border and a bunching effect of the prolabium because it has little chance to grow downward.

Figure 20 *B* shows a case in which repair was done by denuding the maxillary process along lines determined by the battery. The sides of the prolabium were denuded between points measured by the calipers to equal the sides, the prolabium was tunneled and then effort made to directly appose the muscle elements through the tunnel.

Figure 21 shows the plan by which one side is repaired at one sitting and the other side is repaired after a six weeks' or two months' interval. For a long time I deprecated the last method because of its effect on the

premaxilla of the alveolar process. Great pains have been taken to replace this structure, and when the lip is repaired it is immediately displaced. But on the second repair, the premaxilla evidently assumes its former position. The photograph of this patient shows clearly the effect of the lip on the alveolar process cleft. The plan of two operations has recently become more popular with me. The attempt to sew both clefts and replace the ala approaches at times a formidable procedure, and it is a great relief to repair one side at a time. It has been found possible to bring the active elements of the sides to the middle of the prolabium; when this is done the second time it brings these elements almost if not exactly in positive contact. At any rate, the end-results yield motion in the prolabium when stimulated by the battery.

However, the repair illustrated in figure 20 B is more direct and follows the muscle theory more closely, if it can be technically accomplished. In all cases the flaps have been turned into the nostril.

The solution of the problem of repair of a cleft lip is so important for the future comfort and social happiness of the child and it is therefore such an enormous responsibility for the surgeon that these suggestions and reports must be carefully considered before attempts are made to follow the principle.

The arguments for symmetrical contact of the muscle elements appear so logical and so well supported clinically that whatever the technic may be, the steps will be analyzed as to their effect on the muscle elements.

Embryologic and clinical study of the lip indicates two separate principles: muscle repair for the body of the lip; plastic repair of the nostril.

Alveolar Process Cleft.—The statistics on the alveolar process cleft are as follows:

Incidence of cleft ranging from notch to wide clefts			258, or 75.7% of 350
Wired			71, or 27.5% of 258
Vomer cut $\begin{cases} \text{front} & 3 \\ \text{back} & 8 \end{cases}$			11
Undercorrected $\Big\}$ Overcorrected			?

In three fourths of all cases the question of the procedure for the closure of this cleft arises. In all cases I have followed the broad general principle that the cleft in the process is a bone problem. To mobilize bone, force is required, either direct or indirect, or both. The relative merits of each have been discussed in the literature with great diversity of opinion, which ranges from the advocating of direct force through the medium of wires and plates to the view that one should rely on the indirect force of the musculature of the face and specifically

of the lip. In this series both principles have been used and in several combinations, depending on the age of the infant and the degree of the cleft.

The plans may be noted as follows:

1. Molding of alveolar process by thumb pressure; repair of lip at same sitting.
2. Molding of alveolar process; adhesive strap to face; repair of lip delayed.
3. Molding of alveolar process; insertion of holding wire; repair of lip delayed.
4. Molding of alveolar process; insertion of holding wire; repair of lip at same sitting.

1. Molding of Alveolar Process by Thumb Pressure; Repair of Lip at Same Sitting: To report statistically on the degree of the defect would require a description of each case because no two cases are exactly alike, but a broad statement may be made that the defects in a large number of unilateral cases run from 6 to 12 mm. The width of the unilateral cleft is due to the pivotal displacement of the median frontal nasal process, which has united with one or the other maxillary division which is carried along in the pivot. In the bilateral case the measurements have an enormous range with inequality of the sides due to the projectional and rotational displacement of the premaxilla, which is out of contact with both maxillary divisions.

All through the series, whether unilateral or bilateral, a great effort was made to follow plan 1 as the simplest and most direct way, accompanied by a minimum amount of traumatism and reaction. For the notch, in the 2, 4, 6 and possibly 8 and 10 mm. clefts of the alveolar process, there is no debate as to the propriety of this procedure, and it is quite the rule that in clefts of these degrees the cleft is closed by the time the stitches are removed from the lip. The plan has been tried in the wider clefts, 8, 10, 12 and 14 mm., with varying results. If the bones are soft and pliable and the degree of the cleft is easily changed by pressure with the thumb to 4 mm., the cleft in the alveolar process may close early, but more often the change is gradual. On the other hand, the plan has proved incomplete in the wide clefts or in the clefts of the older babies. There are cases in which the alveolar process is not closed over a period of four years.

In the clefts measuring 8 mm. and over, some supplementary step seems to be indicated.

2. Molding of the Alveolar Process; Adhesive Strap to the Face; Repair of Lip Delayed: This plan is as old as the literature on the subject, but has been lost sight of with the development of more elaborate procedures. More recently it has again been used as a preliminary measure to the repair of the lip—a preparation of the bones in order to minimize the loosening of the cheeks which in the wide clefts is necessary to lessen tension caused by the stitch.

There is never an apparent reaction to the procedure; it can be used early and can be repeated often without an anesthetic, in the office or at home. Whenever it is used, constant attention and observation are necessary, because one may be surprised to find that with this simple step overcorrection or overlapping of the margins of the cleft may occur in some cases. However, the tendency is for the bones to spring back into the original condition. The straps must be repeatedly tightened and continually applied up to the time of the operation on the lip, or the purpose will be defeated.

An increasing number of infants have been satisfactorily treated in this manner—infants who in the past would have been subjected to the more formidable operations to be described.

A   B
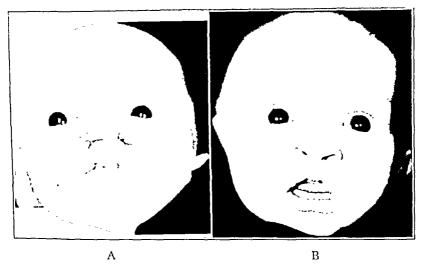
Fig. 21.—Double cleft lip repaired at two sittings, six weeks or two months apart: A, repair of the left cleft; B, repair of the right cleft and final result. The original of this case is shown in figure 24 A.

3. Molding of the Alveolar Process; Insertion of Holding Wire; Repair of Lip Delayed: As a student of the wonderful literature on this subject, I was deeply impressed by the teachings of the late Dr. Brophy. Based on experience in thousands of cases, ingenious plans were promulgated for the use of direct force applied to the upper jaw through the medium of wires and plates. The steps were based on the concept of a whole or a complete cleft palate and the theory that the width of the cleft was due to the lateral separation of the bones. (This is a purely personal interpretation of his principles.) In several cases not included in this series, these plans were used in operating, but were not used in subsequent cases for several reasons:

1. Individual technical inability to apply the wires and plates without seemingly undue traumatism.

2. Observation and study which led to the belief that the width of the clefts was due to the obliquity of the palatine processes in the hard palate plus the odd and bizarre positions of the premaxilla.

3. Occurrence of a cleft palate which was always median in the hard palate and lateral in the alveolar process, but never a straight line complete cleft palate.

4. Overcorrection of the maxillary process and malocclusion with the mandible.

5. The fact that the bone problem lay in the process and not in the hard palate.

In spite of these ideas, I accepted the principle of direct force in any form because the process was normally formed in bone and sug-
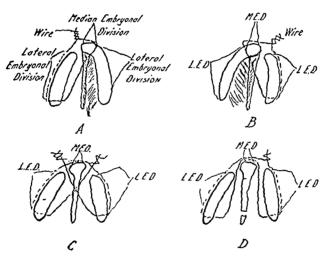
Fig. 22.—Tracings of the various plans offered for the application of direct force to the upper jaw by the use of holding wires. *A* shows the technic in the repair of the right cleft; *B*, of the left cleft; *C*, the combined technic applied to the bilateral cleft, and *D*, circumferential wiring.

gested the use of wires inserted along lines developed for the study of the embryology of this part of the body, illustrated in figures 22 and 23, i. e., direct force applied to the median division only.

The survey reveals that wires were applied in 71 of 258 cases. This was somewhat of a surprise. It appears that I was more interested in establishing the principle than I was in its use.

During a period of trial and error, there were 2 cases in which the wires were applied on an 8 mm. cleft, but most of them were used on the wider clefts, which at the time of the operation, on account of width or rigidity of the bones, could not be brought down through pressure to a point where a lip could safely be sutured with the expectation that it would close the cleft of the alveolar process.

It has never been possible to close the cleft of the alveolar process entirely by such measures (fig. 23 A). To attempt to do so requires undue force which may affect other structures than the premaxilla. When the repair of the lip is delayed, the wires should remain in place until the lip is sutured. In the unilateral clefts (figs. 7 A and B) the results were variable and often not permanent. I have watched these babies over a period of from four to six weeks and have then removed the wires; in two or three days the bones spring back into the original condition just as when plan 2 is used, so that nothing is really accomplished until the lip is repaired.

In cases of bilateral clefts (fig. 7 C) the maxillary divisions appear to me to be always in position with normal occlusion with the mandible, so that the marked deformity is in the median division with the projec-
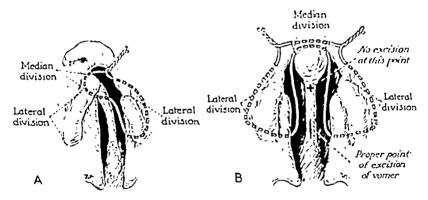
Fig. 23.—A, a formal drawing of the plan for wiring the right or the left unilateral cleft. B, the plan for circumferential wiring of the jaw for the bilateral cleft. The change from the original drawing is that a short wire is used in front in order to get a right and left twist instead of one. The rotation of the premaxilla is more easily controlled.

tion and rotation of the premaxilla. Something must be done to replace this structure in contact with the two sides. In this combination plan 3 has been more satisfactory than in any other case, and apparently is the only way in which the extreme degrees have been successfully treated.

In some cases the projection is great on account of an apparent overgrowth of the septum and vomer, so that it is necessary to section, fracture or remove part of this tissue. Incision or excision in front (fig. 23 B) has been long discontinued, on account of the possibility that growth of the premaxilla may be inhibited. Instead, the base of the vomer is attacked; the wires are placed as in figure 23 B and are left until the injury is apparently healed, when they are removed and the lip is sutured. The immediate effect of such a procedure is shown in figure 24 B.

4. Molding of the Alveolar Process; Insertion of Holding Wire; Repair of Lip at Same Sitting: This procedure has never been used on the bilateral cleft. The repair of the lip is exacting and time-consuming. When two operations are done at one sitting, the patient may become exhausted. Such a consideration as this, here and elsewhere, is another factor in my low mortality rate. In the cases of unilateral cleft there is the best chance of success. In fact, in some cases the alveolar process is closed so promptly that a question is raised as to the necessity of the application of the wire.

Plan 4 is generally recognized. There is a diversity of opinion as to the materials used—silver wire, silkworm gut or soft material, trocars, large or small, straight needles, etc.—and there are different ideas as to points of insertion.
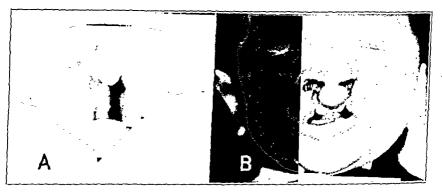
Fig. 24.—Photograph of a successful result in a Group III bilateral cleft in which the premaxilla was subjected to the circumferential wiring by the plan shown in figure 23 B. The end-result of the operation on the alveolar process and lip in this case is shown in figure 21.

The theory on which the application of the wire is based in the unilateral cleft is that the maxilla in contact is displaced outward secondary to the pivot of the premaxilla septum and vomer, and that force should be applied to the median division only in order to replace it on the maxilla out of contact. The wire in front is inserted at the point of union of the premaxilla and the maxillary division and is carried far back on the side out of contact. The point of insertion in front is definite; that at the rear is debatable. The possibility that the six year molar, a structure essential to the normal growth of the upper jaw, may be inhibited has been offered in criticism of the insertion posterior to it, and must be considered. Wherever placed, something to hold the bones in position to facilitate the operation on the lip appears necessary.

Overcorrection of the Alveolar Process Cleft: The matter of overcorrection or undercorrection of the process cleft is reported with a

large question mark. Whatever the plan used, the results have ranged from excellent closures and contours to those that are overcorrected. The wire has caused overcorrection of the short side in the unilateral clefts (fig. 25), while in the bilateral clefts there are extraordinary deformities in 2 cases, 1 of which is shown in figure 26. The penalty of direct force is a deformity which may be irreparable; although orthodontic procedures may result in correction to some extent, this is seldom complete.

Experience leads me again to state that the handling of the cleft of the alveolar process is the greatest problem in this field of surgery and that the solution probably lies in reiteration and emphasis of the dictum of early operation in order to apply properly the indirect force of the lip which in my experience is the only force of permanent effect.
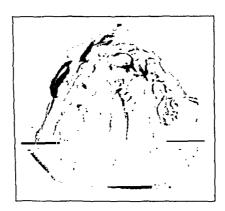
Fig. 25.—The cast of an alveolar process and palate following repair which shows the penalty of the use of the wire on a Group III unilateral cleft. The process of the short side has been moved inward, a situation which results in malocclusion with the mandible. The illustration also shows the successful repair of the hard palate done on plans illustrated in figure 27. The apparent depression of the suture line is in reality a projecting ridge.

I consider the action of the lip to be primary. The wires are accessory to the creation of this force and limited in their use to the extreme degrees of the deformity.

Cleft of the Hard Palate.—The statistics on this cleft follow:

Incidence of inclusion of cleft palate requiring one stitch			272, or 77.7% of 350
No. of cases in which operation was done			199, or 73.2% of 272
No. of operations in 199 cases			244
Primary failures	whole suture line	32	
	front	8	65, or 32.7% of 199
	back	25	
Secondary repair			44
Secondary failure			7, or 16% of 44
Mm. used			15
Lateral incision packed			17

In 77.7 per cent of the cases the cleft of the hard palate is present in either Group II or III. The review of treatment of this cleft is made with a sense of bewilderment. So many technical steps have been suggested for its closure and so many things have been done in this series that a statement of their relative value would be most unreliable. All cases have been attacked on the general principle that this cleft was not a bone problem but one in which some form of a muco-periosteal flap was indicated and that no matter what the arrangement of other tissue in a given case was, cleft of the hard palate was median up to the anterior palatine foramen.

Fig. 26.—A failure of an effort to replace the premaxilla by the plan shown in figure 22 C. The upper cast is of the alveolar process and palate of the boy in the photograph. The lower cast is of the alveolar process and palate in another similar case. In both cases the pressure wires used to force the premaxilla into place acted instead on the lateral divisions, which were moved in behind the premaxilla. In the upper cast the hard palate is shown perfectly united. In the lower cast the hard palate is open owing to tubulation and retraction of the mucoperiosteal flaps, which were severed from the front attachments.

The question of mobilization of bone appears in the literature, but in no case has lateral pressure by wires or invasion of the palatine plates been done. The latter operation has been done on the cadaver with the observation that the plates must be entered on a line mesial to the hamular process in order to move them toward the midline.

Of all the plans offered, the fundamental technical principle has been the classic Warren-Langenbeck operation of lateral sliding flaps mesially sutured.

The objection to this procedure is the formation of a dead space between the bone and the flap, by which infection is invited. The statistical report of approximately 1 failure out of 3 is valid evidence in support of all those who deprecate this procedure and use various other flap combinations. Infection in the hard palate is the main cause of failure. A high temperature may persist after operation (in one case until the tenth day), with the stitches holding, and not subside until some break occurs in the suture line.

In the palates in Group II, on account of the symmetrical arrangements of the tissue there is not the opportunity or the indication for using many of the accessory steps that are possible in the palates in Group III, which may present great variation in arrangement and contact.

As already stated, all steps have been considered accessory to the lateral sliding flaps. These steps are discussed separately.

Lateral Incisions: In nearly all cases the mucoperiosteal flaps have been raised through a small lateral incision (fig. 27 *A*) made in an imaginary line carried forward from a point outside of the hamular process. The incision is made to the bone in order that the inserted elevator may follow the line of cleavage between it and the flap. In the 1/3 and even 2/3 palates of Group II and in the 6 and 8 mm. hard palate of Group III, the flaps are often raised from the margin of the cleft starting in front where the mucoperiosteum is thick and often built up in rugae, and the danger of a button-hole is minimized.

The incision for elevation of the flaps has been used because in the 10 mm. and larger clefts, something must be done to obtain relaxation on account of stitch tension, particularly in the flat arches. This preliminary step may be extended to any degree, from the soft palate to include the hard palate exclusive of the front attachment, a step which has been done but put aside. In all cases the effort was made to preserve the main stem of the palatine artery. Possibly unwittingly this artery has been injured by elevation of the flaps, but ordinarily I believe it is difficult to sever it without direct effort. In the past two years or so the incisions have been extended on the theory that by doing so the median cleft is divided and transferred equally to the sides, and because relaxation permits of the attempt to replace the mucoperiosteal flaps, by thumb pressure, to establish contact with the bone; the dead space is thereby obliterated or at least lessened.

The objection in the literature to the extended lateral incision is that a fistula may form. In no case under my observation has this

occurred. In fact, the usual experience is that these cuts fill in so promptly that often they are healed by the time the baby leaves the hospital.

Packing the Lateral Incisions: I have found 17 cases in which packs were used. The theory of their use is that by packing the dead space,
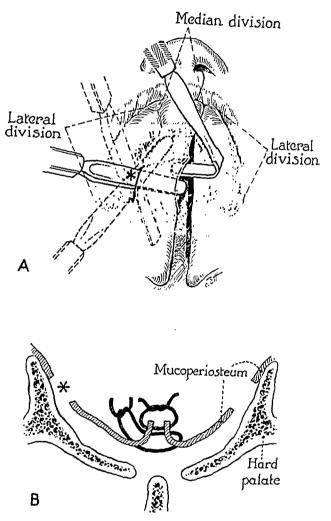
Fig. 27.—*A*, the technic used for repair of the hard palate supplemented by the accessory procedures discussed in the text. *B*, a drawing showing the effort to build the suture line into a raphe.

the upward pull against the stitches and the force of pressure by the tongue are minimized; also, that in some cases, bleeding may appear excessive, and some step appears necessary for safety's sake. In only one case of the whole series did I find a secondary hemorrhage. I found several cases in which a delayed suture of the hard palate had been selected in order to prevent tubulization of the flaps, and packs were

used to hold the flaps in the position until the suture was done. The secondary suture, whether done early or late, is always a difficult procedure in my hands. When done early, the inflammatory reaction present necessitates a most delicate touch, while when it is done late the undercutting of the tube is quite exacting. The packs are gauze strips 1 inch wide. Iodoform, mild silver protein and tincture of benzoin are the chemicals used, with a preference for the last. The objection to the packs is that they soon become foul. I have left them in as long as ten days, but the average time for removal is six days. I believe they are useful in the selected case, but the tendency has been to put them aside in favor of greater relaxation and effort at reposition.

Hamular Process: The arrangement of the tensor palati tissues which loop over the hamular process has led to the suggestion that this structure be fractured to obtain relaxation and facilitate suture and union of the margins of the cleft. For a long time I deprecated this as a destructive and unnecessary procedure. But I have seen it done by expert hands and have done it on the cadaver, during a dissection of these parts. I was much interested to note that the tissues which I interpreted as the tensor palati and the levator palati looked like twin muscles, as though the tensor would assume the function or support the action of the levator. Occasionally in this series the procedure was used, but only in the selected case.

Nasal Mucous Membrane (Vomer): The red tissue over the vomer is wonderfully vital, holds stitches well, can be turned in several ways and appears so resistant to traumatism that apparently in this poor field it might serve as a free graft.

I have turned flaps in two ways: with the base to the mucoperiosteum and again with the base to the vomer.

With the former plan a red line appears in the hard palate, and although this tends to disappear with growth, the result does not have the appearance of a normal palate. In one case, the mucoperiosteal flaps were apparently in contact; the palate was competent to manage fluids, but soft foods appeared at the nostril. At redissection, a complete tube of mucous membrane extending from the root of the vomer up to and into the nose was found. The secondary repair was easy because the mucoperiosteum was in contact but not united. The flap with the base to the vomer is dove-tailed under the mucoperiosteum, seems to lessen the space between it and the bone, holds the mucoperiosteum in place and is greatly to be preferred to the other form.

Delayed Flap: In no case was a turn-over flap, either immediate or delayed, used. In adults or older children this has been used with average success to close holes present through loss of tissue. Early experience with it as a primary procedure was so disheartening that it has been put aside.

Occasionally, as a trial, the front ends of the flap have been cut and the flaps replaced, to be raised and sutured later. The tubulation and retraction have led to a large hole anteriorly, and to the exposure of the septum (fig. 26 B, lower cast). Something must be done to prevent this occurrence, and the best thing is the use of the vomer flap with the base to the bone and dove-tailed underneath, which anchors it in place. Even with this method, I have seen cases with a hole in front. I believe that some front attachment, however slight, should be maintained.

The plan of early secondary suture of the delayed flap has yielded the best results, when it can be followed.

The statistics show that the chance for primary complete union in the hard palate is the lowest offered by any suture line in the body. However, if the holes shown in figure 28, and the hole in front which
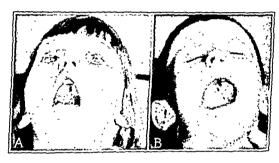
Fig. 28.—*A*, a linear hole which resulted after repair of a Group II-⅔ cleft. *B*, a round hole which resulted after repair of Group III left complete cleft. The hole at the alveolar process cannot be illustrated, but this has been included in the statistics of result under the general head of failures.

cannot be shown, are excluded, possibly my results are not bad when all the factors inimical to a clean wound are considered.

In spite of the report, I still believe that the Warren-Langenbeck principle is acceptable for three reasons:

1. From the study of the embryology, it is the only plan which purports, partly at least, to follow the natural formation of the hard palate.

2. When a primary unit is obtained, the result looks like a normal palate.

3. There is a high percentage of success in secondary repairs.

The trend more recently is to consider the proper season for operation, to inspect the child very carefully, to employ a sequence of operations in the wider clefts and the simplest procedure in the general run of cases with a wide, lateral incision and to give more care and attention to replacement of the flaps, thus taking the two-to-one chance of primary success.

Cleft of the Soft Palate.—The statistics on cleft of the soft palate follow:

Incidence of cleft of soft palate	278, or 77.4% of 350
No. of cases in which operation was done	207
No. of failures	7, or 2.43% of 207
No. of secondary failures	1

It is a great relief to come to the soft palate after the many problems of the other clefts and the great diversity of opinion concerning the steps in their repair.

All patients in this series have been operated on with the idea that the surgical principle is one of muscle repair.

In the literature all operations are based on this principle except one, which fails to recognize that muscle elements disturbed in their
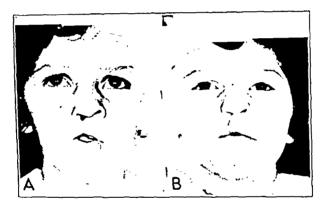
Fig. 29.—*A*, the classic incomplete failure of operation on the lip: a notch at the nostril, a notch at the vermilion border and a short lip, due, I believe, to incomplete union of the musculature of the lip. This photograph is placed here to illustrate my idea that failure of the soft palate to develop may be explained on similar grounds and to emphasize my belief that the problems of the soft palate and of the body of the lip are alike; the prime efforts at repair should be directed to the active elements of those structures. *B*, the results of secondary repair made by the muscle theory operation.

normal relation of origin and attachment must lead to odd or incomplete action and disturbed function.

Excluding this suggestion, all others propose to unite medially and precisely the two halves of the soft palate with the great end in view of normal action of this structure for the purpose of speech and deglutition.

I believe that the many plans attain this result and that they are not different operations but different ways of doing the same thing.

The more recent literature offers some thrilling presentations and discussions on the anatomy, physiology and mechanics of the soft palate.

A new (to me) term of description appears—palatopharyngeal sphincter
—which is so apt to the problem, that I believe it should be accepted and
incorporated in the literature.

In all my cases the effort has been to repair the soft palate as it
was found, in the belief that it was not the length of the palate that was
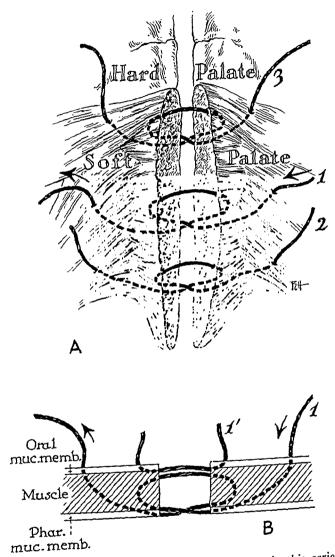
Fig. 30.—Operative procedure used on all soft palates in this series showing
three end-on figure-of-eight stitches, supplemented by single stitches in the mucous
membrane. The only change in the original plans is in the sequence of insertion.
The first stitch is placed in the middle of the palate where a large body of tissue
allows deep and positive bites of the suture and can be used as an anchor for the
further handling of the palate. The second stitch is placed with the small loops at
the top of the posterior pillars. This procedure brings into bold relief the tissues
in the position of the tensor palati, where the third stitch is carefully inserted.

required, but complete and normal action, in order to repair a congenital cleft in a great muscle scheme, which included not only the constrictors of the throat, but those that were indirectly involved down to the larynx.

In fact, the broad general surgical principle in the repair of the body of the lip and the soft palate cleft are considered identical, and each defect is repaired with practically similar operative steps: in the lip, to allow the infant to develop its individual facial expression; in the palate, for control of motion, and in both areas, to coordinate general muscle action. Surgically, the prime effort is precision.

No effort to supplement length has been used because of the belief that if early motion is obtained by a successful union of the sides, the palate will grow along with the body, because the one thing that is known about muscle is that it hypertrophies on use and atrophies on disuse. Failure of the soft palate to develop is most often due, I believe, to inaccurate or incomplete contact of the muscle elements—a situation quite similar to the condition of the lip as shown in figure 29 *A*.

The technic in all cases is illustrated in figure 30 and is briefly discussed in the legend, in which particular attention is called to the slight modification of the sequence of stitch insertion.

The statistics show that the stitches held in 97 per cent of the operations on the soft palate. When one considers all the factors inimical to the primary repair, this is a high percentage, so high that the charts were rechecked. I know that a failure in repair of the soft palate comes as a surprise.

In the 7 cases of operative failure, there are 2 which show loss of tissue. This is a catastrophe, irreparable in most cases, and quite a different effect from a similar result in the hard palate. In the latter, the loss is usually replaced; in the former, secondary efforts have been either unsuccessful or incomplete.

Even though this percentage of success may be exaggerated, it is really high enough for one to say that the question of principles and procedure in repair of the soft palate approaches solution.

CONCLUSIONS

When one considers the time, thought and meticulous care expended on these babies and children, there is a great temptation to view the results through rose-tinted glasses. What I have said in relation to the results obtained in the repair of cleft lips, I wish to repeat in regard to the repair of the other clefts: that the percentages of my successes and failures would be materially altered by the criticism of my colleagues.

The study of these cases reveals that the most satisfactory fields are in the soft palate and the body of the lip. It must be noted that

in each position there are tissues with a wonderful faculty of compensation, and because of this many surgical errors may have been corrected.

The percentage of successful primary results of the operation on the hard palate cleft and the plastic reconstruction of the nostril of the unilateral lip is too low, but I feel that attention to some details of the paper will effect improvement in the future.

The most debatable and unsettled problem is the use of direct force other than pressure with the thumb in the alveolar process cleft. The possible penalty of the use of wire is overcorrection or misplacement and malocclusion. With all the care that I have taken with this possible result in mind, I am free to illustrate my extreme failures. The action of the indirect force of the lip may not close the alveolar process cleft, but the balance is enormously in favor of this plan, because it may easily be supplemented by a prosthesis, while by the use of wires the patient may be subjected to an elaborate follow-up treatment which could have been avoided.

However, the lip may not close the alveolar process in the wider clefts, and the routine use of this force irrespective of degree seems to me to avoid the issue. The answer to this problem probably lies in the age of the patient and an operation, even as a separate procedure, as early as possible in an effort to eliminate the use of wires in favor of the wonderful indirect force of the lip action.

I repeat that the alveolar process cleft is the most important in this field, to be elevated to a peak of consideration as to the age of the patient and the sequence of procedure and of operation in any case.

The statistics reveal that in all cases the clefts of the lip and alveolar process have been operated on at a stated time, i. e., early. Of patients with clefts of the hard and soft palates, only about three fourths have been operated on, which is explained by the more careful selection according to age, degree of cleft and other considerations.

The classification recognizes the importance of the cleft of the alveolar process. In Groups I and II the problems run fairly true to form, but in Group III is added the question: What shall be done to the bone cleft? The classification thus requires the exact literal and pictorial answer to the most important question: What kind of case is it?

Finally, I have found this work the most interesting, intriguing and fascinating of any field of surgery that I have ever studied. The responsibility assumed in the attempt to repair these congenital deformities is quite comparable to that imposed by the major operations on the body, and worthy of the attention of any surgeon. Yet with all this experience and intensive study, I believe with deep humility that there are still many problems that await the touch of a master hand.

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ANATOMIC BASIS FOR THE STUDY OF SPLANCHNOPTOSIS

THE PATHS OF VISCERAL DESCENT; A PRELIMINARY REPORT

AGNES C. VIETOR, M.D.
BOSTON

EN MASSE DESCENT OF THE VISCERA

In ptosis en masse, the abdominal visceral mass moves downward and forward, pushing the incompetent walls before it, without at first causing much change in the interrelations of the viscera, except that the more movable organs tend to descend farther and more rapidly than the less movable ones. This process is seen in its simplest form with the subject lying in the recumbent position when the descent of the diaphragm is insufficiently antagonized (fig. 4, c, in a preceding paper [1]).

In the supine position gravity acts in a ventrodorsal direction, and, for a time, offers an obstacle to mass descent, since it tends to hold the viscera toward their attachments to the posterior wall of the abdomen, while at the same time it reenforces the retaining powers of the anterior abdominal walls (fig. 1 A). In the lateral recumbent position the direction of the action of gravity is so changed that it becomes an additional factor which favors the development of varying phases of both ptosis en masse and individual splanchnoptoses, as well as changes in the body form (fig. 1, E, F and G).

But as soon as the trunk is erected from the horizontal to the vertical —as in changing from the supine to the sitting or standing position—the element of gravity (and its concomitants, traction and pressure) changes from a ventrodorsal to a cephalocaudal direction, and introduces pronounced visceral changes in the incompetent abdomen, regardless of the action of the diaphragm just noted. The retaining power of the abdominal walls is additionally weakened by this new factor, so that the walls themselves all tend to move downward and forward, and to exert traction or pressure in these directions on some of the viscera and on all the rest of the body form (in fig. 1, compare B, C and D with A; compare fig. 2, d, in a preceding paper [1] with fig. 3, a and f, in another paper,[2] showing the same child).

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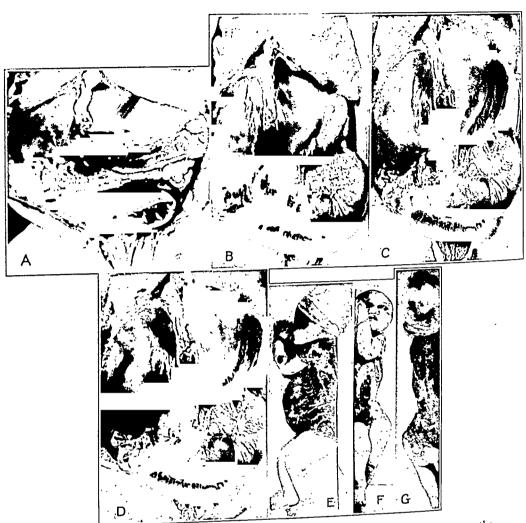
Fig. 1.—The paths of visceral descent due to unantagonized gravity, as the trunk is erected from the supine position to the vertical, in the child at term: *A,* supine position; the attachment of the falciform ligament of the liver to the wall of the upper part of the abdomen is left intact; the stomach is in the second stage of distention; the transparent great omentum is seen thrown upward, veil-like, across the lower half of the transverse colon. *B,* second sitting position (Vietor, A. C.: New England J. Med. **206:**1137 [June 2] 1932). *C,* flexed standing position. *D,* extended standing position. In *B, C, D,* note the progressive retraction of the walls of the thorax and the forward swing of all the abdominal viscera, the traction on the falciform ligament, the descent and swing to the right of the stomach (its development of the pipe bowl shape being hidden by the left lobe of the liver [fig. 4, *E*]), the descent of the spleen (visible to the left of the stomach and descending in a tongue-shaped process over the splenic flexure) and the traction on the stomach by the descending transverse colon, the stress being shown conveyed along the vessels of the gastrocolic ligament. *E, F, G,* marked ptosis en masse in the lateral recumbent position in a child at term, showing the resultant changes in the body form. *E,* view taken from above. *F,* view taken from in front. *G,* view taken from behind.

Moreover, as soon as the upper and lower extremities begin the stretching and elongation of the vestigial, biologically contracted deep fibrous tissues which bind them to the trunk, one of the first results is an increased sacrolumbothoracic anterior convexity which rotates the pelvis forward and downward, projects the viscera forward, causes stress on the abdominal walls and favors descent of both the walls and the viscera.[2] These changes begin in the supine position (Vietor,[2] fig. 2, i), but reach their maximum in the extended standing position (Vietor,[1] fig. 3, a).

Finally, all positional changes in the abdominal viscera are, sooner or later, reflected in the thoracic viscera and in the body form (fig. 3, D and E).

Traction on and by the viscera is largely exerted through peritoneal folds, between the layers of which run the visceral blood and lymph vessels and the visceral nerves. When the viscera are in their normal relations, these peritoneal folds are folded up and relaxed (fig. 1 A), but when the individual viscera are displaced, the folds tend to become opened out; traction then tends to be exerted directly on the visceral vessels and nerves, and thence to be conveyed distally to the visceral masses and proximally to the larger vascular trunks and to the larger neural trunks and ganglions (fig. 1, B, C and D). Traction tends to cause both arteries and veins to elongate and to diminish in caliber, the veins tending to flatten and collapse owing to their thinner and less resistant walls. And one has at present the known sensory effects of traction on the mesenteries in the opened abdomen and also the sensory, motor and trophic effects of traction on external nerves to guide one in questioning as to the more subtle, but undoubtedly far-reaching, effect on the visceral nerves and ganglions. The vascular changes are striking when in the child at term pressure and traction are seen to be especially exerted on the abdominal aorta and ascending vena cava by the unantagonized sacrolumbar anterior convexity which is suddenly developed by changing the lower extremities (thighs) from their spontaneous position of flexion, abduction and outward rotation to the advanced human position of extension, adduction and inward rotation so that the patellae look forward.[2] Such vascular interference, even if occurring slowly enough to permit of gradual changes in growth, suggests a causative factor in the more or less marked general nutritional changes which so often tend to occur in cases of ptosis en masse of the gravity type (Vietor,[1] fig. 3, b).

DESCENT OF INDIVIDUAL VISCERA

The most easily displaceable individual viscera are the kidneys, the stomach, the redundant portions of the colon, the liver, the lungs and the heart.

DESCENT OF THE KIDNEYS

In ptosis of the kidneys these organs, and the suprarenal glands to which they are attached, are projected forward from the depths of the paravertebral fossae to enter on the lumbo-iliac inclined planes which have a more or less steep ventrocaudal direction. Then the kidneys begin their independent descent, the suprarenal glands remaining behind but elongating and showing evidence of stress from the continuing traction exerted by the descending kidneys.

All the laterally placed viscera tend to lie in the long paravertebral fossae, but in ptosis en masse the shape and capacity of these fossae become modified by the descent of the viscera and the synchronous retraction of the posterior and lateral walls of the body.[1] From the broader central region of the trunk, these fossae narrow more or less as they continue downward. They also change their direction, passing ventrocaudad in an inclined plane to terminate at the level of the fourth or fifth lumbar vertebra, though their continuance into the iliac fossae is more or less suggested, especially when the pelvis is rotated backward. These lumbo-iliac inclined planes are strongly marked mediad by the forward projecting bodies of the related vertebrae, the masses of the psoas muscles and the medial portions of the quadratus lumborum muscles, structures which form the median boundary of the so-called kidney niches (fig. 2 *A, a, b* and *c*).

Owing to the relative shortness of the lumbar spine and to the relatively larger size of the kidneys at term, the lower poles of these organs at this stage of development lie only a little above the posterior crests of the ilia.[3] As a result, the kidneys lie more or less on these lumbo-iliac inclined planes which are directed more or less ventrocaudad in proportion as the pelvis is rotated forward or backward (fig. 2, compare *A* and *B*). As the child grows, the lumbar spine lengthens, and the kidneys appear to ascend (though their upper poles remain at the same level), thus resting higher and higher on the lengthening lumbo-iliac planes, the inclination of the latter decreasing from below upward. Thus the kidneys enter more and more into deeper parts of the paravertebral fossae, and they also rotate more and more backward and mediad on a relatively longitudinal axis, so that they come to lie a little obliquely, the hilus and its structures remaining the more anterior. Hence, other things being equal, the greater the breadth and depth of the paraver-

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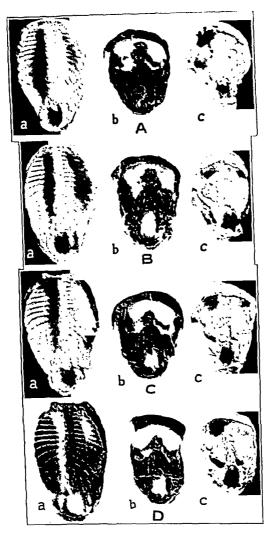
Fig. 2.—The paths of descent of the kidneys due to unantagonized gravity, as
the trunk is erected from the supine position to the vertical, in the child at term:
A, supine position, the lower extremities in spontaneous flexion, abduction and
outward rotation. *B*, supine position, the lower extremities extended, adducted
and rotated inward so that the patellae look forward; *C*, flexed standing position.
D, extended standing position. In *B* and *D*, note the marked tension of the psoas
iliacus muscles, the forward projection of the lumbar vertebrae, the forward rota-
tion of the pelvis and the consequent forward thrust of the kidneys and supra-
renal glands; *a* indicates the paravertebral fossae, showing the lumbo-iliac inclined
planes and the basic foundation for the so-called kidney niches; *b*, the so-called
hepatic, gastrosplenic and kidney niches and the lumbo-iliac inclined planes after
removal of the kidneys, the suprarenal glands being left in position; the diaphragm
is in the position of expiration, the domes sagging a little at their lowest parts;
c, progressive stages in the descent of the kidneys as the lower extremities are
extended, adducted and rotated inward so that the patellae look forward and as
the trunk is erected from the supine to the standing position.

tebral fossae (reflected externally in the loins), the greater is the security of the kidneys in their position, and conversely.

But even at the greatest height and depth attained by the kidneys, the lumbo-iliac inclined planes offer ever ready paths favoring the descent of these organs. The extension cephalodorsad and the downward and forward inclination of these inclined planes are controlled largely by the sacrolumbothoracic anterior convexity which follows, more or less, the normal evolution of the lower extremities (thighs), as these pass from the position of flexion, abduction and outward rotation, existing at birth, to the more advanced human position of extension, adduction and inward rotation so that the patellae look forward.[2]

Even in the supine position, this anterior convexity (lordosis) is thus developed in proportion to the persistence of the vestigial contractions binding the extremities to the trunk, through failure of the postnatal antagonizing mechanism. And as it develops, the psoas iliacus muscles become tense and are thrown into strong relief; the loins are narrowed and dragged forward, and the pelvis is rotated forward and downward; the ventral inclination of the lumbar end of the lumbo-iliac inclined plane is increased; the base of the so-called renal "niche" is lifted as the twelfth and eleventh ribs become part of the inclined plane and as the paravertebral fossa shallows and narrows; while the kidney is rotated forward from without inward, is projected forward as a whole and, especially in its lower portion, now lies definitely on the always present lumbo-iliac inclined plane (fig. 2, *B, a, b* and *c*).

When the trunk is erected to the vertical (sitting or standing position), thus changing the action of gravity from ventrodorsad to cephalocaudad, the latter factor alone, unless the compensating mechanism develops equally, may now begin or accelerate the actual descent of the kidneys (fig. 2, *C* and *D*). Hence, ptosis of the kidneys, either alone or as a part of ptosis en masse, may begin in the recumbent position (fig. 1, *e, f* and *g*; Vietor,[1] fig. 4, *c*) or in the first sitting position (Vietor,[1] fig. 2, *a* and *b*), and it tends to increase, with increase in the conditions favoring it, through the second and third sitting positions (Vietor,[1] fig. 2, *c* and *d*) and through the standing positions (fig. 2, *C, a, b* and *c*), tending to reach its maximum in the extending standing position (fig. 2, *D, a, b* and *c*).

The preparatory step in the production of nephroptosis in even a normally placed kidney is, then, a forward projection of the kidney which lifts it out of its so-called niche in the paravertebral fossa and places it directly on the lumbo-iliac inclined plane. This preparatory step may be accomplished without disturbing the interrelations of the kidney and the suprarenal gland (fig. 2, *A* and *B*), since both the suprarenal glands and the kidneys are projected forward by the same factors, i. e., by increased anterior convexity of the lumbar spine (lordosis) and

by insufficiently antagonized descent of the diaphragm, these two factors acting separately or in combination.

The essential step in nephroptosis is separation of the kidney from the suprarenal gland and independent descent of the former, leaving the latter attached to the diaphragm and other structures. Normally, there exists a relatively loose combination of posterior peritoneum, fascial envelop and fatty envelop, within which the kidney has always some motion, and it is in connection with these tissues (from which it makes a ptosis pouch) that it can slide easily and extensively, downward and forward on the lumbo-iliac inclined plane, into varying degrees of ptosis (fig. 2, *C* and *D*). As the kidney is projected forward, it reverses its earlier backward and mediad rotation, the hilus becoming less and less relatively anterior. And in proportion as it separates from the suprarenal gland it rotates downward and outward, changing the direction of its long axis to downward and inward so as to approach, or even reach, the horizontal, and stretching and elongating the structures of its hilus and its connections with the suprarenal gland, on all of which it exerts traction.

EXPERIMENTAL DATA

Experimental Development of Nephroptosis.—Nephroptosis of the diaphragmatic type can be developed experimentally in the supine position within a few minutes, either in connection with ptosis en masse or individually. In the former case, the abdomen is not opened, and all the viscera remain in situ, the abdominal walls in the dead subject being incompetent within the limits of their fibrous tissues; under such circumstances, only the end-results can be demonstrated (Vietor,[1] fig. 4, *c*). In the latter case, the abdomen is opened and the other viscera are removed so as to expose the undisturbed suprarenal glands and kidneys; the various steps can then be studied in sequence, as they progress to the same end-results, respiration being simulated by intermittent inflation of the lungs.

As the insufficiently antagonized diaphragm descends more and more deeply under pressure of the intermittently inflated lungs (which continue to hold more and more residual air), the suprarenal glands are drawn forward and upward on the pillars of the diaphragm to which they are attached, and they are seen to pucker all over in moderately fine puckerings which seem to involve the entire depth of their substance. The kidneys follow the suprarenal glands forward, and as they are thus projected, they reverse their earlier backward and mediad rotation, and the hili become less and less relatively anterior. At the same time, the kidneys move downward and outward from the suprarenal glands, being pushed in these directions by the elastic pressure of the descending domes of the diaphragm against their upper poles. Thus, as they descend, they rotate downward and outward as on a relatively anteroposterior axis, the upper poles diverging and the lower poles converging. Coincidentally, the kidneys exert pressure and traction on their enclosing structures, so as to produce ptosis pouches; the process is similar to that occurring in the gravity type of ptosis, which is to be described next, though in a lessened degree. These processes continue until the kidneys are so far detached from the suprarenal glands as to be no longer within reach of the pressure of the descending diaphragm, when the direct action of the diaphragm

Figure 3.

Fig. 3.—Details of intermediate stages in ptosis of the kidneys: *A*, ptosis of the kidneys as part of ptosis en masse, showing the displacement more marked in the right kidney than in the left. The liver, stomach, and left portion of the transverse colon are held up by mattress sutures to reveal the kidneys in situ. The right kidney is largely separated from the suprarenal gland and is rotated downward and outward so that its long axis approaches the horizontal. The traction exerted on it by the ptosed right portion of the transverse colon and the overlying pressure exerted by the liver are clearly shown. The left kidney is just emerging from beneath the suprarenal gland, and its long axis has begun to be directed obliquely downward and inward, while its freedom from direct traction and pressure contrasts strongly with those factors on the right. *B*, all the abdominal viscera are removed except the liver, the suprarenal glands and the kidneys. The liver is then drawn upward, pulling the suprarenal glands and the kidneys upward and forward, and throwing into strong relief the ptosis pouches formed by the descending kidneys as they separate from the suprarenal glands, pushing before themselves the posterior peritoneum and the anterior portions of their fascial and fatty envelops. The kidneys have been freed from their adhesions to the suprarenal glands and to the pouches, to show the more advanced stage of ptosis when they hang suspended from the structures of their hili (compare with *D*). Their long axes are now practically horizontal, and their lower poles overlap in the median line. Note the flattened, triangular, tongue-shaped continuations of the posterior perirenal and pararenal fat, which slide downward behind the posterior peritoneum. Note also the ptosis of the lungs and of the heart: *C*, supine position; view taken from above. The thoracic and abdominal viscera are in position, as found at term, the lungs being artificially inflated to counteract the retraction ensuing on opening the pleural cavities. The transparent, veil-like structure thrown over the transverse colon is the great omentum. *D*, extended standing position, view taken from in front. The kidneys were displaced as a part of the gravity type of ptosis en masse. Then the other abdominal viscera were removed; the ptosis pouches of the kidney were opened, exposing their interiors, and the kidneys were freed and allowed to descend as far as the structures of their hili permitted. The thorax was then opened, and the heart and lungs were found displaced and showing the changes characteristic of advanced ptosis en masse of the gravity type. The pericardium was not opened. Note the marks of traction shown by it, by the mediastinal tissues and their extensions upward and by the thymus. Note that the left lung tends to fall lower than the right, to a greater or less degree. *E*, same subject as in *D*. No change was made except to lower the subject to the supine position, thus changing the direction of gravity from cephalocaudal to ventrodorsal (view taken from above). The right lung is displaced from in front to show how the posterior border expands medially, thus helping to hold the heart forward. Otherwise, there is return of the heart and lungs to approximately their original conditions, with disappearance of the evidences of traction and stress. Note the returning shortening and broadening of the thoracic cavity and its viscera, as well as of the abdominal cavity. Note the return of the kidneys and of the elongated and stretched suprarenal glands toward their original positions.

Figure 4.

Fig. 4.—The paths of descent of the stomach, in varying stages of distention, when exposed to insufficiently antagonized gravity in the extended standing position. *A*, the stomach is in the second stage of distention, and it has already descended. Note the narrowing and elongation as the cardia is approached, the accompanying descent of the narrowed and elongated spleen to the left and the traction by the descended transverse colon on the body and antrum of the stomach, the first portion of the duodenum, the transverse fissure of the liver and the neck of the gallbladder. The gastrocolic ligament became detached from the stomach between the vertical wrinkle shown and the point of contact of the left border with the spleen. Note how the persisting traction to the right of this area interferes with the normal upward and forward rotation of the stomach which begins in this stage (compare with *E*, and note how traction on the stomach by the transverse colon is lessened, as in this case, when the latter is empty and when it finds support, as on the cushion of distended small intestines). *B*, in addition to the liquid present, the stomach is inflated with air sufficiently to carry it to the beginning of the third stage of distention, the edge of the left side of the thorax being lifted by a suture to show the gastrosplenic niche. Note the migration of the stomach downward, forward and to the right, as well as the marked rotation upward and forward and the kinking on both the gastric and duodenal sides of the pylorus, while the outlines of the antrum tend to merge more definitely with those of the body and to suggest a form of telescoping of the former into the latter. *C*, inflation is carried further, so as to develop a later phase of the third stage of distention, the stomach migrating still farther downward, forward and to the right, the antrum moving toward assuming an anteroposterior direction, and the first portion of the duodenum moving toward kinking and torsion, as it becomes hidden by the antrum and body of the stomach. Note the increased descent of the spleen as it lies on the splenic flexure. *D*, inflation is carried still further so as to develop the fourth stage of distention, the stomach approaching the limits of its migration downward, forward and to the right, and adding a second upward and forward rotation. The antrum is directed backward, or even a little from right to left, and it tends to press the pylorus or the adjacent part of the first portion of the duodenum against the posterior wall of the abdomen, and to cause obstruction of the stomach or duodenum, or of both. The spleen continues to move downward, forward and to the right with the stomach. In this case, the low density of the distending contents partly antagonizes the localizing effect of gravity, the stomach falling more gently throughout, in contrast with the stomach in *E*. *E*, same subject as in figure 1, *A* to *D*, in which the stomach contents are of greater density. The liver is held up to reveal the stomach which shows that the effect of gravity is not only diffused generally, but is especially localized in the lowest part of the body of the stomach, the tissues yielding and developing the pipe bowl shape of stomach, and impairing the upward and forward rotation belonging to this stage of rotation (second to third). Note the kinking at both ends of the antrum (which maintains its direction upward and to the right, due in part to the frustration of this upward and forward. rotation. *F*, the liver is experimentally rotated backward and to the right, causing descent of the transverse fissure, the lesser omentum, the antrum and the first portion of the duodenum and developing an approach to what has been called the "tubular" type of stomach. The experiment is favored in this case by the pressure of a distended large loop of the subgastric transverse colon which nearly fills the left hypochondrium by displacing the stomach into, or to the right of, the median line. Note the greater visibility of the transparent great omentum in this case, as compared with figure 1, *A*, owing to the greater deposits of fat along the lines of the blood vessels.

on the kidneys ceases (Victor,[1] fig. 4, *c*). As the kidneys descend, they make traction with each inspiration on the connections uniting them with the suprarenal glands, this traction being conveyed to the latter organs through their fibrous framework, and producing the puckerings seen externally. If the lower extremities (thighs) are first extended, adducted and rotated inward so that the patellae look forward, the consequent forward projection of the lumbothoracic spine, the kidneys and the suprarenal glands, facilitates the separation of the kidneys from the suprarenal glands.

Nephroptosis of the gravity type can be developed experimentally a little less speedily but, nevertheless, quite rapidly (fig. 2, *A, B, C* and *D;* fig. 3, *A, B, D* and *E;* fig. 4, *A* and *E*). In addition to gravity acting in the downward and forward direction of least resistance, the initial force from behind to project the kidney forward is in this case not the diaphragm, though this element may be added, but the sacrolumbothoracic anterior convexity which tends to develop as the trunk is erected to the vertical, and which is increased in the extended standing position as the lower extremities are at the same time extended, adducted and rotated inward so that the patellae look forward. Both the suprarenal glands and the kidneys are carried forward, the latter again rotating forward and mediad and also descending and making traction on the former, but the traction is now continuous instead of intermittent, and instead of puckering the suprarenal glands it causes them to elongate and to be dragged after the descending kidneys. This causes traction stress on the suprarenal glands which is conveyed through them to their basic attachments to the diaphragm and other structures, but these attachments do not yield, and the suprarenal glands remain in their relative position.

As the kidneys become separated from the suprarenal glands and descend, they also begin to rotate downward and outward as on a relatively anteroposterior axis, the upper poles diverging and the lower poles converging. Thus, the long axis of the kidney, from being directed downward and outward, becomes first vertical and then inclined more and more obliquely downward and inward, as it moves toward the horizontal, eventually approximating, or even reaching, that position.

As the kidney moves caudad, away from the suprarenal gland, it pushes before itself the anterior leaf of its fascial envelop (covered in part by the posterior peritoneum) as well as the related portion of the perirenal fatty envelop, and it thus develops a pouch in which it lies, this ptosis pouch gradually broadening below and collapsing above as the kidney descends, still rotating outward as it descends, so that its long axis continues to move toward the horizontal. This pouch is sharply delimited laterally by the union of the anterior and posterior leaves of the perirenal fascia, and it is definitely delimited below, though the anterior and posterior leaves of the perirenal fascia do not here directly merge. They are, however, united to each other by a special arrangement of strong fibers of connective tissue which extend through the perirenal fat and form what has been termed a "basket" (Kelly and Burnam) below the lower pole of the kidney.

While the ptosis pouch of the descending kidney is thus formed largely by the stretched and elongated anterior leaf of the renal fascial envelop, with the related portion of the perirenal fat, the posterior leaf of the renal fascial envelop shares in the descent by elongating and sliding downward on the posterior abdominal wall without definitely leaving the latter. Hence, it is the posterior leaf which appears to be the stronger, either intrinsically or through its connections, or perhaps both. In any case, it bears the brunt of the traction exerted by the descending kidney, and, in turn, beyond the limits of its yielding to this stress, it transmits the traction to the posterior abdominal wall. The continuations of both the peri-

renal and the pararenal fat below the kidney also slide downward, forming two flattened, triangular, tongue-shaped masses of fat, with apexes directed downward, which advance below the descending kidney down the iliac fossa and along the lateral brim of the pelvis, pushing before them the overlying posterior peritoneum. These sliding triangles of fat are more or less sharply delimited from each other and from the mass of the descending kidney (fig. 3, *B* and *D*).

By combining the displacing action of unantagonized gravity in the standing position and that of insufficiently antagonized descent of the diaphragm, the complete cycle of nephroptosis can be developed experimentally in a very short time. It can be compared with the autoproduction of a demonstrable advanced nephroptosis in the unopened abdomen in the standing position in the following case: A tall, slender woman, aged 26, has ptosis en masse of the gravity type. She states that she had subjected herself to marked tight lacing for several years. During that time, her right kidney was said always to be prolapsed. Since her marriage, two years ago, she has given up lacing, and now the kidney is often not easily palpable. She can bring it into evidence by standing and throwing her trunk to the left side and backward, arching the left side of the trunk. This flattens the lumbosacral region and throws the right pelvis up and forward, flares the right lower ribs and makes the right side of the abdomen prominent. She then increases the intra-abdominal pressure by taking quick, deep abdominal inspirations and by making slow, forcible expirations, each accompanied by a downward expulsive effort concentrated toward the right side of the abdomen. As she proceeds, the right kidney emerges from beneath the liver and ribs and can be plainly followed by the hand as it travels down to the pelvis and backward and forward across the right side of the abdomen. The patient reports repeated attacks that answer the description of ureteral colic.

In the gravity type, if the ptosis pouch and other related structures are not too stretched and lax, the assumption of the supine position tends to encourage the kidneys to slide upward and backward, along the lumbo-iliac inclined planes, toward the suprarenal glands and toward the primary location of the structures of their hili (fig. 3, compare *E* with *D*). If the related structures are too lax thus to guide it, the kidney remains floating in some part of the abdomen, and it may, more or less, even cross the median line (fig. 3, *B* and *D*).

In the diaphragmatic type, the return of the kidneys in the supine position is hindered by the tendency of the diaphragm to remain lowered, even during expiration, owing to the tendency of the ptosed lungs to become emphysematous, and to the tendency of the diaphragm to become lowered, broadened and shallowed (Vietor,[1] fig. 4).

Intrinsically, the two kidneys, their envelops and their immediate attachments react in the same way to the same laws, but the right kidney tends to descend more easily and to a lower level than the left. This is the result of several extraneous factors: 1. The colonic and primitive mesenteric evolution of the right side of the abdomen takes place later than that of the left and, consequently, is less complete and stable; as a result of this condition, the colonic and primitive mesenteric surroundings of the right kidney give less stability and support, and permit more pressure and traction, which favor descent (fig. 3, *A*). 2. Other abdominal viscera exert a displacing power on the right kidney which they do not exert on the left, and a retaining power on the left kidney

which they do not exert on the right (fig. 3, *A*). 3. Some of the ultimate attachments of the right kidney are longer or less resistant than the corresponding ones of the left kidney, and some of the ultimate attachments of the left kidney are shorter or more resistant than the corresponding ones of the right kidney (fig. 3, *B* and *D*).

In all cases, when the other abdominal viscera are left in situ, the right kidney descends more easily and rapidly than the left (fig. 3, *A*). In all cases, when the other abdominal viscera are removed, and only the kidneys and suprarenal glands are left in situ but undisturbed, the two kidneys descend similarly, sometimes the left being momentarily the lower; but ultimately, when (on opening the enclosing pouches and freeing the kidneys from their adhesions to these pouches and to the suprarenal glands) the two kidneys hang swinging on the elongated structures of their hili, the right tends to hang lower than the left (fig. 3, *B* and *D*).

DESCENT OF THE STOMACH

In ptosis of the stomach, the fundus remains under the left vault of the diaphragm; the organ as a whole struggles to rotate upward and forward, and to migrate downward, forward and to the right, and conversely, as it is distended and emptied; the antrum remains high at its junction with the first portion of the duodenum, but eventually the walls of the body yield and descend below the level of the antrum to form the bowl of the typical "pipe-shaped" stomach.

EXPERIMENTAL DATA

The marked normal mobility and the varied positional changes observed in this study as the stomach passes from the empty to the distended condition and back to the empty or resting position have been described in detail.[3] It will suffice now to note that under distention the first change is the separation of the anterior and posterior walls from each other, the organ remaining in position (first stage of distention). Then, if the distention is continued and increased, the stomach balloons out in all directions and migrates from its recess (gastrosplenic niche of left paravertebral fossa) behind the left lobe of the liver and under the left dome of the diaphragm where, however, the fundus remains, the path of migration being determined by the inclined plane which bounds the gastrosplenic niche medially and antero-inferiorly. As it migrates, it rotates on varied axes, at first forward and upward (second stage of distention, fig. 4, *A*), then also downward, forward and to the right (third stage of distention, fig. 4, *B* and *C*), and, finally, again forward and upward (fourth stage of distention, fig. 4, *D*). Then, as its distention subsides, it passes through these changes in reverse order and retracts until it lies, with anterior and posterior walls in apposition, in its original location and in its empty or resting shape and position (Vietor,[3b] figs. 6 and 7). These physiologic changes of position and contour must be differentiated from ptosis, though the path of descent of the stomach in ptosis is largely determined by this physiologic basis.

All the hollow abdominal viscera have the common peculiarity that as they are distended they tend to swing on their mesentery and to rotate forward and upward, the degree of rotation (other things being equal) depending on the density of their contents, being greatest when this is least. A structure which in this sense acts toward the stomach as the regular mesentery does toward the intestines is the lesser omentum (gastrohepatic omentum or so-called gastrohepatic ligament), and it is on this peritoneal fold that the stomach swings in its normal movements of distention and retraction (though in the initial upward and forward movement, which is more definitely limited to the body of the stomach, i. e., in the second stage of distention, the rotation seems to occur more definitely on the abdominal esophagus and the gastrophrenic ligament, fig. 4, *A* and *E*).

And it is on this peritoneal fold, and on the structures which it encloses, that traction is markedly made when it is unfolded by the descent of the stomach in ptosis. The distal attachments of this gastrohepatic mesentery are the central tendon of the diaphragm (from the neighborhood of the esophageal opening) and, passing to the right, the transverse fissure of the liver. The support of the stomach is continued to the left of this gastrohepatic mesentery by the abdominal esophagus, the gastrophrenic ligament and the gastrosplenic omentum, as well as by the direct (nonperitoneal) attachment of the cardia and fundus to the diaphragm; and it is continued dorsad by the great vascular trunks which run so short a course before being distributed to the stomach and related viscera. Traction by the descending stomach is exerted on all these structures, including the related nerves and ganglions.

The one outstanding factor in ptosis of the stomach is the relative resistance which this line of attachment offers to the traction exerted on it by the descending stomach, the tissues of the stomach themselves eventually yielding under the stress (fig. 4 *E*). It is important to note that the attachment of the lesser omentum is continued to the right beyond the limits of the antrum of the stomach, so as to include the first portion of the duodenum (fig. 4, *A*, *B* and *E*); the resistant powers of this and of related nearby structures are well shown by the observation that even in advanced gastroptosis the duodeno-antral region remains high, the firmer antrum suggesting a stem on which the flaccid body of the stomach hangs and sags, the body tending to elongate and to develop the familiar pipe-bowl-shaped stomach, with kinking tending to develop at one or at both ends of the antrum, i. e., in the softer body of the stomach or in the softer first portion of the duodenum (fig. 4, *B* and *E*). It is further important to note that when this duodeno-antral portion of the lesser omentum is unfolded and subject to traction, the latter force is expended also on the important structures which are enclosed within

its folds as they enter or emerge from the transverse fissure of the liver, i. e., the hepatic artery and vein, the bile ducts and the portal vein, together with lymphatic vessels and nerve plexuses (fig. 4, *A, B, C, D* and *E*). And when the cysticocolic ligament exists as an extension of the lesser omentum, the traction is thus extended to the neck of the gall-bladder (fig. 4, *A, B* and *C*).

Although the fundus remains under the left dome of the diaphragm, as the stomach descends traction is made on the abdominal esophagus, which tends to elongate and to narrow. There is a similar tendency to elongation and narrowing of the cardia and, indeed, of the whole body of the stomach, as a result of the traction which is thence conveyed to its diaphragmatic attachments (fig. 4, *A* and *E*).

The fundus and body of the stomach and the spleen lie in what may be called the gastrosplenic niche, in the sense in which the lungs, the liver and the kidneys lie in niches, all these recesses being parts of the paravertebral fossae (fig. 2, *A* to *D;* fig. 3, *C, D* and *E*). This gastrosplenic niche in its upper portion forms a more or less deep and broad concavity which lodges the spleen, the fundus and most of the body of the stomach (fig. 4, *B, C, D* and *E*), while its lower and more median portion forms an inclined plane which is directed downward, forward and mediad, and which consists of the left suprarenal gland and kidney, the left portion of the pancreas and, still more deeply, the posterior portion of the diaphragm separating the abdominal and thoracic cavities (fig. 2, *A, B, C* and *D*). It is on this inclined plane that the lower part of the body of the stomach and the antrum lie, though the latter may pass on or over the projecting front of the vertebral bodies to unite with the first portion of the duodenum. Above and on the left side, the gastrosplenic niche is bounded by the left lobe of the liver and by the left dome of the diaphragm, the splenic flexure of the colon and the transverse mesocolon being interposed below (fig. 4, *A* to *E*). On the median side the niche is limited by the vertebral column and by the posterior angles of the related ribs, being separated from these structures by the diaphragm and by the left pleural cavity, while the lesser curvature is continuous with the transverse fissure of the liver through the gastrohepatic omentum (fig. 4, *A, B, C* and *D*).

Not only is the stomach subject to descent through the influence of insufficiently antagonized gravity and descent of the diaphragm, which cause it to exert traction on its supporting attachments, but it is also subject to traction from below; this added traction tends to increase its descent and its former traction as well as the yielding of its own tissues. The added traction is due to descent of the transverse colon and is exerted through the gastrocolic ligament whenever this peritoneal fold is less deep than is the corresponding portion of the transverse meso-colon (fig. 1, *B, C* and *D;* fig. 4, *A, B* and *E*). Thus, another force is added toward producing gastroptosis, and particularly the pipe-bowl-shaped stomach (fig. 4, *A* and *E*). And as the subgastric transverse colon is always more or less redundant [3] (Vietor,[3b] table 1), traction by

it on the stomach, through the gastrocolic ligament, is always potential when the abdomen is incompetent.

In this study, the gastrocolic ligament at term has been found to vary greatly in depth (from about 1 mm. to practically the same depth as that of the transverse mesocolon), and this variation is not uniform in all portions, being deeper, for example, in the redundant loops of the subgastric transverse colon than in the nonredundant portions. It has also been found that, regardless of other redundancies of the transverse colon, the most constantly redundant loop tends to lie below the vicinity of the external border of the resting or empty stomach,[a] this redundancy seeming to be related to the normal excursions in mobility of the stomach as it passes from emptiness to distention and back to emptiness.

The So-Called Tubular Stomach.—In this study, descent of the duodeno-antral region occurred only when the liver was rotated backward and to the right, and this descent favored the development of what has been called the tubular type of stomach (fig. 4 *F*). This tubular appearance seemed more strongly suggested when the stomach was of the pyriform rather than when it was of the quadrangular type (Vietor,[3b] figs. 7, 9-XLVI and 5-XLIX).

Relation of the First Portion of the Duodenum to Movements of the Stomach.—The proximal part of the first portion of the duodenum is movable, and it shares more or less in the movements of the stomach, thus permitting the stomach to move farther to the right, or forward, or upward or downward, as it migrates during distention,[3b] and at the same time tending to produce kinking, torsions, or obstruction of the duodenum. As the stomach descends in ptosis, it still struggles during distention to pass through the cycle of changes described, but as it falls, there is a greater tendency to develop kinking at the junction of the body and the antrum, as well as kinking and torsion of the first portion of the duodenum (fig. 4, *B, C, D* and *E*), with increased tendency to develop obstruction at the pylorus or just distally to that point (compare fig. 4 *D* with figs. 7, 9-XLIIB and 9-XXXVII in a preceding paper [3b]).

CLINICAL QUESTIONS SUGGESTED

Remembering the marked tendency to the development of ulcer along the lesser and greater curvatures of the stomach, and on both the gastric and duodenal sides of the pylorus, one cannot help but question whether the traction on the regions here demonstrated may not at least predispose to the development of such lesions. Other things being equal, the gastric lesions would be expected to occur more often in the smaller eaters, whose stomachs would be more likely to be limited to the earlier phases of distention (the first, second, and early third stages), and who would be thus more directly exposed to simple insufficiently antagonized gravity and traction; while the pyloric and duodenal lesions should be more frequent in the larger eaters, whose stomachs would be more likely to pass through the more advanced phases of distention (the more advanced third and the fourth stages),

which tend more definitely to involve the region of the pylorus and the first portion of the duodenum in torsion, as well as in kinking, traction and obstruction.

Also, as one notes the ease with which obstruction of the stomach or of the first portion of the duodenum may be produced at term by overdistention of the stomach (the later third and the fourth stages [3b]), which causes the antrum, with or without the movable part of the first portion of the duodenum, to assume an anteroposterior direction and press the pylorus or the adjacent first portion of the duodenum against the posterior abdominal wall, one cannot but question whether a so-called "congenital hypertrophy of the pylorus" may not rather often be an acquired condition (fig. 4, *D*; compare with figs. 7, 9-XLIIA, 9-XLIIB and 9-XXXVII, in a preceding paper [3b]).

PTOSIS OF OTHER ORGANS

Spleen.—As the stomach descends, it makes traction on the spleen and exposes the latter organ more definitely to the action of insufficiently antagonized gravity. As a result, the spleen descends in a tonguelike process which extends downward to the left side of the descending stomach, apparently being guided by the sustentaculum lienis (left phrenocolic ligament) to slide on or over the splenic flexure (fig. 1, *B, C* and *D;* fig. 4, *A* to *E*).

Colon.—In ptosis of the nonredundant colon, this portion of the intestine tends to move downward, forward and mediad, making traction on, and elongating, its mesocolon or attachments, and tending to develop or to increase angulation, kinking and stasis. In ptosis of the redundant colon, the loops readily unfold, introducing at once the variable problems of migration and torsion; of traction on the vessels and nerves of their mesocolon and intervisceral connections, and on the continuations and attachments of these structures; and of kinking and stasis at the angles of the loops.

The nonredundant colon follows the lines of parietal attachment of its mesocolon in outlining, a little irregularly, the circumference of the posterior and posterolateral walls of the abdomen (Vietor,[3b] fig. 8). The redundant colon follows parietally the same lines of mesocolon attachment, but its mesocolon varies in depth and its redundant tissue forms loops (Vietor,[3b] fig. 9). These redundant loops are found in prenatal life and at term in one of two conditions: They are either more or less folded up along the lines of the parietal attachment of the mesocolon (fig. 1 *A;* fig. 3 *C;* fig. 4 *A* and *F*), or else they are more or less unfolded and directed, predominantly. toward the midabdomen (fig. 1, *B, C* and *D;* fig. 4 *E*).

Thus, an unfolded intestinal loop cannot necessarily be considered an example of ptosis. It would seem, rather, that ptosis might be considered to begin when the abdominal walls are so incompetent to support the unfolded loop, either directly or indirectly, that traction is exerted on the mesocolon or on intervisceral or parietal attachments.

Though migrations and displacements may at times cause some variation, the unfolded loops of the transverse colon tend to be directed downward; the sigmoid colon, upward; the subhepatic, downward, forward and inward; and the ascending and descending colons, forward and inward and perhaps also downward (Vietor,[3b] figs. 4, 5, 9 and 10).[3]

The position of the colon and its loops is also modified by the degree of support and counter-resistance offered by the abdominal walls, by the degree of distention which they undergo and by the density of the distending contents. When distended, the colon has a tendency to rotate on its mesocolon eccentrically to the midabdomen; in such case, the loops tend to migrate upward, or upward and outward, especially if the density of the contents decreases, though gravity tends to make them descend, especially if the density of the contents increases. Thus, the transverse colon may at any moment swing upward and be found projecting forward at any angle to the vertical; it may overlap the free margins of the right or left lobes of the liver, or it may even be found filling the left part of the hypochondrium, compressing the stomach, displacing it toward the right, and causing it to make lateral traction on the abdominal esophagus (fig. 4 F).

In the vertical positions (sitting, standing), gravity tends to cause the redundant loops of the transverse colon to fall downward and forward and toward the midabdomen; the loops of the sigmoid colon tend to fall and to become displaced (especially toward the right) and to form new arrangements,[3] and those of the ascending and descending colons tend to swing forward and downward.

As the transverse colon descends, it makes more or less traction on its attachment to the posterior abdominal wall and to the intervening viscera, either directly or through the transverse mesocolon, the former being especially characteristic of the right portion as it crosses the second portion of the duodenum and the right kidney (fig. 3 A; fig. 4 A). The left portion would similarly make traction on its mesocolon, but it tends first to make traction on certain intervening viscera whenever the intervisceral connections are shallower than is the transverse mesentery. These intervening viscera are the stomach, the first portion of the duodenum and the neck of the gallbladder, and the traction is made through the gastrocolic, the duodenocolic and the cysticocolic ligaments [3b] (fig. 3 A; fig. 4, A, B, C, D, E and F).

As the redundant loops are unfolded, kinking may occur at one or at both ends of the loops, interfering with both peristalsis and antiperistalsis and leading toward stasis. This tendency is modified in proportion as the angles at the ends are distended; hence traction, kinking, and stasis are most pronounced when emptiness of the angles coincides with fulness of the body of the loop (Vietor,[3b] figs. 4, 5 and 16).

The small intestine is surrounded by the large intestine. When the former is distended, it moves forward on its mesenteric anchorage and extends eccentrically in all directions, proportionately to the density of its distending contents and to other factors. It thus tends to exert pressure, eccentrically, on the surrounding large intestine and to form an elastic cushion on which rest the transverse colon and mesocolon, the liver and the distended stomach (fig. 3 C). If distention of the large intestine is added, the latter rotates further on its mesocolon, eccentrically to the midabdomen; the abdomen is enlarged in all directions, and the transverse colon may be found thrown upward over the liver and stomach, or encroaching on the latter in the depth of the left part of the hypochondrium, or even (if the gastroduodenocolic ligament is shallow enough) making upward traction on the stomach and first portion of the duodenum, and perhaps even on the neck of the gallbladder.

Liver.—In ptosis of the liver, this organ, like the fundus of the stomach, does not leave its position under the domes of the diaphragm; hence, as it descends under the influence of insufficiently antagonized gravity, the diaphragm, the walls of the thoracic cage and the lungs retract to follow it, the ribs becoming oblique as they fall, and all three of the latter structures diminish proportionately in lateral expansion during inspiration. These changes in the surroundings of the liver explain why its ptosis may not be confirmed by percussion of the parietes, since as the organ descends, the enclosing parietes also descend, at the same time retracting, especially laterally. Again, somewhat similarly to the body of the stomach, the tissues of the liver themselves may yield under stress, so that the organ may tend in time, wholly or partially, toward elongation and change in contour (fig. 1, compare B, C and D with A; note E, F and G).

The liver is held in position in apposition with the domes of the diaphragm not only by its attachments but also by a negative pressure resembling that noted in the articulations, and within the limits of its attachments it seems to move physiologically somewhat as does the head of the bone within a ball and socket joint. These movements are varieties of limited rotations on varied axes and have been called versions. The rotations may be forward, backward or laterally, or in combinations of these directions, and they seem to be in the nature of adaptations to the other viscera and to the parietes. The first change which the liver undergoes in ptosis is in the direction of more or less exaggeration of these physiologic movements. When the abdominal walls are relaxed, and even in the supine position, the liver tends to sag toward the right, in the direction of its heavier lobe, making more or less traction in that direction on all its connections, both visceral and parietal (fig. 1 A). This sagging to the right is increased in the right lateral recumbent

position (fig. 1, *E* and *F*), but it is progressively decreased as the trunk is raised toward the vertical, in the sitting (fig. 1 *B*) and standing positions (fig. 1, *C* and *D*). In the extended standing position, this inclination to the right tends to be further neutralized by the increased forward thrust of all the viscera (following the increased sacrolumbothoracic anterior convexity which is due to the extension, adduction and inward rotation of the lower extremities), and also by the visceral pull being directed more and more downward and forward as the direction of gravity becomes more and more cephalocaudad; the increased forward thrust now makes all the viscera still more responsive to gravity and they tend more and more to fall downward, forward and mediad (fig. 1 *D*).

The sagging to the right (right lateral version) seems to be determined by the weight of the larger right lobe, and it seems to be more or less operative in all relaxed positions and to be conveyed to the left lobe till checked by the falciform ligament. Aside from this sagging to the right, the first step in ptosis of the liver due to insufficiently antagonized gravity is a forward rotation (anteversion), and when the abdomen is opened its degree is plainly marked by the appearance of the whitish, sodden, peritoneal surface which in the supine position had been in prolonged contact with the domes of the diaphragm. In its descent, the right lobe tends to be retarded by the right kidney and by the right half of the transverse colon and to come to rest with its lower edge on the small intestine (especially if the latter is distended), the hepatic flexure, the sustentaculum hepatis when present, and, perhaps, the adjacent ascending colon. The left lobe appears to be less firmly attached than the right and more easily displaceable, though following similar paths of anteversion and movement to the right, progress in the latter direction meeting evident limitation at the falciform ligament (fig. 1, *B, C* and *D*).

Backward rotation of the liver (retroversion) occurs whenever the posterior portion of the organ is depressed from above or whenever the anterior portion is elevated from below. It is one of the changes which may occur in the second, or diaphragmatic, type, of ptosis en masse,[1] and it may occur temporarily, at any time, as the result of excessive distention of the intestines or stomach. In experiments here made, it has been the only factor found capable of lowering the first portion of the duodenum and its connection with the antrum, so as to produce the so-called tubular type of stomach (fig. 4 *F*).

Ptosis of the liver (especially the forward movements of rotation and descent) is antagonized directly by competence of the upper part of the abdomen, but if the lower part of the abdomen is incompetent, the downward movement may continue with its resulting traction

(gravity type of ptosis en masse [1]). On the other hand, if the lower part of the abdomen is competent and the upper part, incompetent, the downward movement tends to be modified and the forward movement emphasized, with resultant modification of traction (on the diaphragm, the thoracic viscera and the wall of the body) and pressure, the forward movement making toward epigastric projection and expansion of the subcostal angle (diaphragmatic type of ptosis en masse [1]).

When the liver is lifted, upward traction is made on all the abdominal viscera, and in a contrary sense, all the abdominal viscera thus have a potential capacity for traction on the liver. The most fixed portion of the liver is posteriorly where the inferior vena cava is attached to it, and just below the point at which this large vessel penetrates the diaphragm to enter the right auricle. Hence, this is the ultimate point of resistance in ptosis of either type which affects the liver.

Lungs.—In ptosis of the lungs, these organs descend by elongation or other changes in shape, as the thorax shares in the changes in body form and in the action of the diaphragm due to ptosis en masse.

Always filling the closed pleural cavities in which they lie free, the lungs expand in all directions from their anchorage at their hili, according as the enlarging movements of their limiting parietal boundaries permit, these boundaries being the thoracic cage and the diaphragm (fig. 3 *C*).

Hence, the descent, retraction, flattening, elongation and changed action of the boundaries which have been demonstrated as the result of the first or gravity type of ptosis en masse mean the descent, retraction, flattening, elongation and changed action of the lungs (fig. 3, compare *D* with *E*; compare with fig. 3, *b*, in a preceding paper [1]). Similarly, the descent, flattening, broadening, shallowing and forward projection of the diaphragm, the increased anteroposterior diameter of the thoracic cage, with increasing downward and forward obliquity of its axis, and the changed action of these boundaries, which have been demonstrated as the result of the second, or diaphragmatic, type of ptosis en masse, mean corresponding changes in the position, shape and action of the lungs (Vietor,[1] fig. 4, *c*).

These changes in the surroundings of the lungs explain why their ptosis may not be confirmed by percussion of the parietes, since, as these organs descend, the enclosing parietes also descend. In this study, the left lung and the left dome of the diaphragm appear to descend more readily than the right, this change seeming to be related to the more ready descent of the left lobe of the liver (fig. 1, compare the thorax in *B, C* and *D* with that in *A*).

Heart.—In ptosis of the heart, this organ tends to rotate downward and from left to right toward the median line, the apex leading and the portion to the right of the median line also moving mediad.

Lying free in the closed and fixed pericardium, the heart has its anchorage in what might almost be called its hilus, which consists of its continuing afferent and efferent vessels and nerves. The pericardium is broadly attached to the central tendon of the diaphragm and is continued upward for a short distance on the large vessels at the base of the heart, being continuous also with the hili of the lungs, and with the upward continuing structures of the mediastinum and its other viscera. The central tendon of the diaphragm is the highest portion of this muscle, and it gives the impression of being held up by the mediastinal tissues even when the lateral domes fall lax and descend (fig. 3, *D* and *E*). Both the central tendon and the mediastinal tissues are very firm in their consistency, and they stretch or fall only under the influence of great stress, showing comparatively slight change even when the lungs and heart show profound changes. This degree of stress seems to develop as the thorax retracts, narrows and elongates in ptosis en masse.

The left dome of the diaphragm is lower than the right, and it also tends to descend more easily, and under the stress of ptosis en masse the left side of the heart, which is also the freer portion, tends to follow it, the apex leading (fig. 3 *D*). As the ptosis progresses, the heart rotates, as it were, from left to right and from above downward, on its fixed mediastinal base, appearing more and more elongated and narrowed, and suggesting a tubular shape. At the same time, the heart to the right of the median line similarly retracts, but a little from right to left, toward the attached base (fig. 3, compare *D* with *E*). The heart also tends to fall backward, the retracted and narrowed chest walls, which narrow the posterior planes as well as the anterior ones, tending to antagonize and make more difficult not only the backward expansion of the lungs, but also the mediad expansion of the posterior margins, the latter expansion normally pushing and holding the heart forward in the chest, as especially shown on the right side in fig. 3 *E*.

The degree of traction and stress exerted progressively through these changes on the cavities of the heart and on its afferent and efferent vessels is evident. Less evident, but just as definitely to be traced, are the traction and stress on the hili of the lungs and on all the connected and related viscera and tissues which extend upward, that on the thymus and its connections showing particularly clearly in fig. 3 *D*.

SUMMARY

1. The fundamental step in splanchnoptosis is incompetence of the abdominal walls, due to failure in the development or coordination of the complex reflexes through which the muscles of these walls support the viscera by antagonizing gravity, overdescent of the diaphragm and persistence of the vestigial binding of the extremities to the trunk.

2. The next step is forward projection of the viscera and shallowing of the paravertebral fossae. This forward projection of the viscera marks the preparatory stage of splanchnoptosis. The next step is the essential stage of descent of the viscera and of traction on their intervisceral and parietal attachments, on their nerves and blood and lymph vessels, and on the related body walls. All changes in position of the viscera cause corresponding changes in the body form.

3. The viscera may be displaced en masse, or individually or in varying combinations. No organ or structure is exempt, but the most easily displaceable individual viscera are the kidneys, the stomach, the redundant portions of the colon, the liver, the lungs and the heart.

4. When the kidneys and suprarenals are projected forward, they enter on the lumbo-iliac inclined planes which furnish direct and inviting paths for descent. As the kidneys descend, they separate from the suprarenal glands, the intervisceral attachments elongating and making traction on the suprarenal glands which, themselves, elongate but remain fixed. Traction is also made on all the structures of the hili.

5. The distending stomach normally finds a descending oblique plane which guides it downward, forward and to the right, though its fundus remains under the left vault of the diaphragm. Ptosis occurs to a greater or less extent along the same path, but continuing descent causes elongation of the body of the stomach, the lower part of this portion descending below the antrum which remains high, thus developing the characteristic pipe bowl shape.

6. The movable part of the first portion of the duodenum tends to share in the movements of the antrum. and it may undergo traction, pressure, kinking, torsion or obstruction.

7. The spleen tends to descend with the stomach and to elongate, its lowest portion becoming tongue-shaped and extending downward and forward on the splenic flexure.

8. The transverse colon is always more or less redundant, forming one or more loops. When the loops are unfolded. they tend to descend, to exert traction on their attachments and to cause kinking and stasis at their angles. Even a moderate descent may cause traction on the stomach, the first portion of the duodenum and the neck of the gall-bladder.

9. The liver remains under the right vault of the diaphragm, but, within the limits of its attachments, it is subject to forward, backward and lateral rotations. When the traction on its attachments exceeds its limitations, its tissues yield, and it becomes wholly or partially elongated or otherwise modified in shape.

10. The lungs always remain attached at their hili but descend by elongation or by other changes in shape, as the thorax shares in the changes in body form and in the altered action of the diaphragm due to ptosis en masse.

11. The heart, through the pericardium and the other firm mediastinal tissues, remains attached to the structures at its base, but it tends to rotate downward, and from left to right, toward the median line, the apex leading, and the portion to the right of the median line also moving mediad.

INFLUENCE OF CONGESTION ON TUBERCULOSIS

O. R. HYNDMAN, M.D.

AND

HARRY LANDT, M.D.

IOWA CITY

About ninety years ago Rokitansky[1] observed a marked inconspicuousness of pulmonary tuberculosis in passively congested lungs. He asserted that diseases of the heart and of the blood vessels producing passive congestion of the lungs are a preventive of phthisis. How these observations led Bier to introduce as a therapeutic measure the artificially produced passive hyperemia that now bears his name is a matter of history.

Since the reports of Rokitansky, many able clinicians have been impressed by the favorable influence on tuberculosis of cardiac or pulmonary diseases which invoke passive congestion. They likewise have been impressed by the unfavorable influence of diseases which are associated with hyperventilation of the lungs. Among those who have made definite comment on these phenomena are Osler, Weiss,[2] Walsh,[3] Fishberg,[4] Hoffmann,[5] Brügelmann and Sewall.[6] Certain pathologic states, such as mitral stenosis and cardiac decompensation, are definitely associated with chronic passive congestion of the lungs. Weiss expressed the opinion that in mitral stenosis pulmonary tuberculosis is infrequent as a result of the venous congestion. Fagge's postmortem record shows 4 cases in thirty years, and according to Kidd's statistics the incidence of mitral stenosis in tuberculosis is 1 in 500. Walsh observed that cardiac decompensation and active tuberculosis do not develop concurrently.

Certain pathologic states, such as pulmonary stenosis and hyperthyroidism, are provocative of a situation in the lungs which is the opposite of congestion—that is, hyperventilation. Osler stated that

1. Rokitansky: Handbuch der pathologischen Anatomie, Vienna, Braunmüller u. Seidel, 1844, vol. 2, p. 520.

2. Weiss, A.: Wien. klin. Wchnschr. 25:697, 1912.

3. Walsh, J.: Am. Rev. Tuberc. 6:975, 1922.

4. Fishberg, Maurice: Pulmonary Tuberculosis, Philadelphia, Lea & Febiger, 1916.

5. Hoffmann, F. A., in Nothnagel, C. W. H.: Diseases of the Bronchi, Pleura and Lungs, Philadelphia, W. B. Saunders Company, 1903, p. 241.

6. Sewall, H.: Occult Tuberculosis, Am. Rev. Tuberc. 3:665 (Jan.) 1920.

all forms of congenital heart disease, particularly pulmonary stenosis, predispose to tuberculosis. It has been observed that tuberculosis has a very unfavorable course in exophthalmic goiter.

Rokitansky thought that pulmonary emphysema and tuberculosis maintain a relationship of mutual exclusion, and Brügelmann felt that a person with asthma is immune to tuberculosis. Reports of cases have been made in more recent times, however, which lessen the strength of these two opinions. Malone,[7] though stating that bronchial asthma coexisting with tuberculosis is relatively infrequent, reported: that in 157 cases of bronchial asthma, 18 per cent of the patients had tuberculosis as shown by roentgen examination, though there was no mention of the activity of the lesion (Manges and Hawley) ; that in 20 cases of asthma with tuberculosis, the sputum gave positive reactions in 10 (Pollak), and that in 189 cases of asthma, 3 per cent of the patients showed tuberculosis (Unger). There is some dispute, however, as to whether pulmonary emphysema and bronchial asthma are always productive of or associated with passive congestion of the lungs.

In tuberculosis of tissues other than the lungs, Bier's congestive hyperemia is believed to be beneficial. Its use, particularly in tuberculosis of the joints, skin, bones and thecae of the hand, is advocated in modern textbooks on surgery. Laënnec felt that tubercles and cyanosis are antagonistic. Though great benefit and sometimes a cure have been attributed to the congestion, no adequate explanation has been made for the phenomenon.[8]

Thus an experimental problem presents itself concerning the influence that chronic passive congestion may exert on the initiation and progress of tuberculosis. Since the favorable influence which has been observed clinically has been attributed to increased carbon dioxide concentration, it is within the province of such an investigation to determine the effect of varying concentrations of the commoner atmospheric gases on the tubercle bacillus in vitro.

We have been able to find only two references to animal experimentation on this subject, that of Levinson and Peterson and that of Corper and Goldberg, to which we shall refer in the report of our work with guinea-pigs.

Though ligation of the pulmonary artery has been done in human beings as well as in experimental animals,[9] no one, to our knowledge,

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7. Malone, J. T.: Bronchial Asthma and Tuberculosis, U. S. Vet. Bur. M. Bull. **4**:222 (March) 1928.

8. Da Costa, J. C.: Modern Surgery, General and Operative, ed. 8, Philadelphia, W. B. Saunders Company, 1919, p. 260.

9. Lilienthal, H.: Thoracic Surgery, Philadelphia, W. B. Saunders Company, 1925, vol. 2, p. 484. Bruns: Beitr. z. Klin. d. Tuberk. **24**:253, 1913.

has tried ligation of veins as a therapeutic or experimental measure. Arterial ligation is reported to have little or no influence on tuberculosis.[10]

We feel that information on this problem not only is important in connection with a possible application in the surgical treatment of pulmonary tuberculosis but is pertinent to a consideration of the favorable factors attending pulmonary collapse.

CULTURE OF THE TUBERCLE BACILLUS IN VITRO WHEN SUBJECTED TO VARYING CONCENTRATIONS OF OXYGEN, CARBON DIOXIDE AND NITROGEN

In 1918, Wherry and Ervin [11] observed and performed several experiments to show that the growth of a culture of the tubercle bacillus was completely inhibited when carbon dioxide was absent. The carbon dioxide was removed by sodium hydroxide to which the culture tube was connected. They observed that concomitant with the growth of the organism the supply of oxygen in the culture tube was depleted, but there was usually enough oxygen in a small closed test tube to yield a confluent layer of growth. During the growth, carbon dioxide was elaborated. When they subjected a culture to 13 per cent carbon dioxide in one tube, no growth was obtained.

In 1921, Corper, Gauss and Rensch,[12] considering these findings significant, extended the studies. They observed that 3 per cent carbon dioxide caused some inhibition of the growth of tubercle bacilli and that 15 per cent was tuberculocidal. They confirmed the fact that the bacillus fails to start initial growth in an atmosphere free from carbon dioxide. Cultures of tubercle bacilli were buried in the tissues of living animals and so arranged that the author felt that the gases in the tube would come into equilibrium with those in the tissues. The latter were controlled by buried tubes to which atmospheric air was allowed ingress. The completely buried cultures were inhibited as compared to the controls. They found that in a closed tube after the carbon dioxide elaborated by the growing bacillus reached a concentration of 5.5 per cent growth was inhibited. On the basis of these results they felt that the concentration of carbon dioxide normally existing in the human body is sufficient to inhibit definitely the growth of tubercle bacilli and that this factor is extremely significant in resistance to the disease.

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10. Van Allen, C. M.; Nocoll, G. L., and Tuttle, William: Lung Changes After Occlusion of Pulmonary Artery Branches by Embolus and by Ligature, Yale J. Biol. & Med. 2:363 (May) 1930.

11. Wherry, W. B., and Ervin, D. M.: The Necessity of Carbon Dioxide for the Growth of B. Tuberculosis, J. Infect. Dis. 22:194, 1918.

12. Corper, H. J.; Gauss, Harry, and Rensch, O. B.: Resistance to Tuberculosis: A Non-Immunologic Chemical Factor Worthy of Consideration, J. A. M. A. 76:1216 (April 30) 1921.

In 1925, Novy, Roehm, Soule and Novy, Jr.,[13] carried out detailed and elaborate experiments in the study of microbic respiration with a direct application to the tubercle bacillus. A known strain of human Bacillus tuberculosis was used. The culture medium was an agar base with glycerin, dextrose or serum.

Some of the results obtained were as follows:

1. From 100 to 150 cc. of oxygen (or its equivalent, from 500 to 700 cc. of air under normal cultural conditions) must be provided in order to obtain a rich growth. The yield of carbon dioxide was slightly less than the amount of oxygen consumed, as much as 150 cc. of carbon dioxide being produced by a single culture. When the bacilli were grown on glycerin agar, the respiratory quotient (corrected) was 0.836.

2. In an ordinary closed culture tube the oxygen was removed in a few days by the inoculum, and no visible growth resulted. (Therefore in an effectively sealed tube absence of growth or slow growth means an insufficient supply of oxygen.) When all of the oxygen (20.9 per cent) was consumed by the culture the carbon dioxide yield reached 17.5 per cent. Thus, as the respiratory quotient was less than 1 and some carbon dioxide was dissolved in the medium, considerable negative pressure was developed.

3. Growth occurred with any oxygen concentration, the optimal value being from 40 to 50 per cent. With a concentration of 100 per cent, growth developed as isolated, thick, moist, white colonies which at the end of fifty-eight days were infective. At a very low oxygen tension the growth was retarded but continued until "the last atom of oxygen was consumed."

4. In atmospheres containing from 10 to 50 per cent of carbon dioxide growth was not inhibited. When the concentration of carbon dioxide was 60 per cent or more, there was some inhibition, but fair growth was obtained in 90 per cent carbon dioxide. A culture which developed in from 85 to 96 per cent carbon dioxide for fifty-nine days was viable and infective.

5. Continued removal of carbon dioxide from the culture tube by alkali did not stop growth. The experimenters felt that any inhibition under such conditions was due to desiccation by the alkali, since moisture is an important factor in securing rich and even growths.

On the basis of these results, the conclusion was drawn that the slow multiplication of the tubercle bacillus in the body is explainable from the standpoint of growth in the presence of diminished oxygen tension. An indefinite supply of oxygen under a tension corresponding to a few millimeters of mercury will probably enable the organism to

13. Novy, F. G.; Roehm, H. R.; Soule, M. H., and Novy, F. G., Jr.: J. Infect. Dis. **36:**109 and 343, 1925.

grow, though very slowly. Rest and a rich diet in checking the progress of the disease probably act by reducing to a minimum the available oxygen supply in the tissues.

Up to this time the results of these two investigations had stimulated authors to place emphasis on entirely different phenomena with regard to the influence of atmospheric gases on the tubercle bacillus. Corper emphasized the inhibiting influence of carbon dioxide while Novy emphasized the inhibiting influence of an atmosphere poor in oxygen.

In 1927, Corper and his co-workers [14] observed that in their experimental animals the lungs were involved to a greater extent after the intravenous administration of tubercle bacilli than were other organs, particularly the liver. In attempting to find an explanation for this on the basis of gaseous tension, he repeated and modified his former in vitro work. The sealed test tube method was abandoned, and the gas mixtures were arranged to flow constantly over the cultures from large feed tanks. By this method Corper observed no inhibitory effect of carbon dioxide on the cultures until a concentration of 54.5 per cent was reached. On the contrary, concentrations of carbon dioxide greater than that in air and as high as 14 per cent seemed to have a stimulating effect on growth. Oxygen was again found necessary for growth, and cultures were inhibited in very low concentrations. No growth was obtained in 0.1 per cent oxygen in six weeks. Cultures were then submitted to atmospheres the gaseous composition of which was that of alveolar air and that of mixed venous blood. The figures for mixed venous blood were taken from L. J. Henderson and were: carbon dioxide, 47 mm. tension (7.48 per cent), and oxygen, 35 mm. tension (5.57 per cent). For alveolar air they were: carbon dioxide, 40 mm. tension (6.37 per cent), and oxygen, 100 mm. tension (15.94 per cent). The tubercle bacilli grew better in the atmosphere of alveolar air than in the gases of mixed venous blood, and thus Corper felt it fair to assume that they should grow more rapidly in the lungs than in the spleen, kidneys and bone marrow and in all these organs more rapidly than in the liver.

He stated further that conditions which can change the oxygen tension in tuberculous foci from 0.7 to 3.8 mm. may be sufficient to change a quiescent focus into progressive disease. One of the most important single factors influencing the oxygen tension is the hydrogen ion concentration of the blood by its effect on the dissociation of oxyhemoglobin. Fatigue and starvation cause an increase, while rest and nourishment cause a decrease, in available oxygen in this way.

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14. Corper, H. J.; Lurie, M. B., and Uyei, Nao: The Variability of Localization of Tuberculosis in the Organs of Different Animals: III. The Importance of the Growth of Tubercle Bacilli as Determined by Gaseous Tension, Am. Rev. Tuberc. **15**:65, 1927.

At first we were led to believe that the inhibition of our cultures in sealed tubes was due to high concentrations of carbon dioxide, but further experiments proved conclusively that this was not the case. Our results bear out the conclusions that oxygen must be available or the growth will cease and that concentrations of carbon dioxide as high as 38 per cent will not materially inhibit the growth. A small amount of carbon dioxide is necessary for initial growth to take place.

The virulent Gluckson strain of B. tuberculosis was used in the in vitro and in part of the animal experiments.[15] We used Corper's gentian violet-glycerin-potato medium for all in vitro experiments and subcultures.
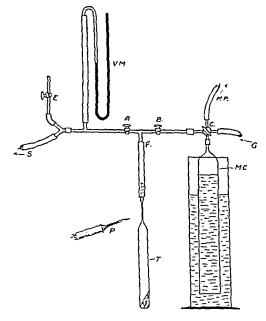
Fig. 1.—By manipulating the threeway stopcock (C.), mercury is drawn up to the capillary mark in the neck of the graduated mixing cylinder (M.C.) by means of the mouthpiece (M.P.). The desired gases are then allowed to flow in through G., the mercury levels in the chamber and the reservoir being kept equal while readings are taken. With stopcocks E. and C. closed and A. and B. open, the gas in the culture tube (T.) is sucked through S. until a near vacuum is produced. This is indicated when the vacuum manometer (V.M.) presents equal mercury levels. (A water suction pump will fail to produce a complete vacuum by at least the vapor tension of water, but for our purpose this was negligible.) With A. closed and B. and C. open, T. is filled with the mixture. The gas in T. is again sucked out, and after two or three such washings the tube is finally filled with the mixture under atmospheric pressure and the capillary neck quickly sealed with a hot pencil flame (P.).

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15. The Gluckson strain of B. tuberculosis was supplied to us by H. J. Corper.

EXPERIMENTS

After inoculation of the potato medium contained in 1 by 10 inch test tubes, the necks of the tubes were pulled out so that they fitted

TABLE 1.—*Results of Experiments A, B and C*

Experiment A

Date of Inoculation: 10/12/31   Date of sealing: 10/12/31   Tubes opened: 12/7/31

Nitrogen, per Cent	Carbon Dioxide, per Cent	Growth After 56 Days*	Comment
99	1	0	After six weeks, the tips of the tubes were broken, and the cultures were incubated for another six weeks in free communication with air; the medium became too dried out to be of any value though growth had developed in the tubes containing 7 and 15 per cent carbon dioxide
98	2	0	
97	3	0	
96	4	0	
95	5	0	
93	7	0	
85	15	0	
70	30	0	
50	50	0	
100	0	0	
Control.............................		++++	

Experiment B

Date of Inoculation: 10/12/31   Date of sealing: 10/12/31   Tubes opened: 12/7/31

Oxygen, per Cent	Nitrogen, per Cent	Growth After 56 Days	Growth After Communication with Air (6 Weeks)
2	98	0	?
5	95	Trace	+++
10	90	0	++
50	50	0	?
75	25	0	?
95	5	0	?
100	0	0	?

Control: Medium became too dried out to be of any value

Experiment C

Date of inoculation: 9/11/31   Tips of tubes broken and cotton stoppers
Date of sealing: 9/11/31   inserted: 11/10/31 (60 days)

Oxygen, per Cent	Carbon Dioxide, per Cent	Growth After 60 Days	Growth After Communication with Air (6 Weeks)
0	100	0	+++
50	50	+	+++
70	30	++	+++
80	20	+	++++
85	15	0	++++
90	10	0	+++
95	5	++	++
96	4	++	++++
96	4	+++	+++
97	3	++	+++
97	3	+++	++++
98	2	+++	+++
98	2	++	+++
99	1	0	+++
99	1	0	++++
100	0	++	+++
Air	..	++++	
Control	..		

* In all the tables the amount of growth is represented in the customary manner as being from + to ++++, the latter being maximum.

tightly in a piece of ordinary suction tubing. An apparatus (fig. 1) was designed for the evacuation of the tubes. They were subsequently filled with the desired gases from the mixing chamber and then sealed with a pencil flame blow torch. The cultures were incubated at 37.5 C.

for at least six weeks. (A definite error must be admitted in the mixing of the gases, but this did not prove to be of relative importance under the circumstances of the experiment.)

The results of experiments A, B and C are shown in table 1. The best growth was obtained in from 2 to 5 per cent carbon dioxide. After subsequent exposure to air for six weeks, only the tube containing 100 per cent carbon dioxide failed to show growth. In all of the tubes except the one containing air the bacilli grew in isolated, large, umbilicated colonies. Sometimes abundant growth occurred in the fluid at
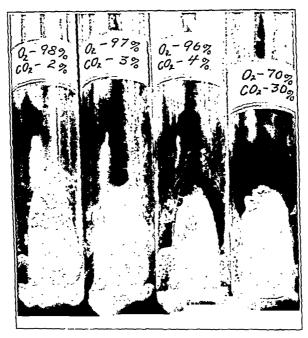
Fig. 2.—Photographs of cultures in high oxygen tensions, showing the character of growth in large, isolated, crater-like colonies. The abundant growth in the fluid at the bottom may be seen in the tube containing 97 per cent oxygen and 3 per cent carbon dioxide.

the bottom of the tubes (fig. 2). Novy obtained the same result in high concentrations of oxygen and since such a characteristic growth does not occur in any concentration of carbon dioxide when the oxygen tension is low, we feel that it can be attributed to high oxygen tension.

Experiments D and E (table 2) indicate an unexplained irregularity in results when the gas mixtures are imposed on cultures which have already attained an initial growth. The only explanation that we can offer for this is that organisms which have already attained a growth cannot adapt themselves to sudden marked changes in gaseous tension.

When the tips of the tubes were broken, our attention was called to the negative pressure which had developed in some of the tubes. We then measured the negative pressures and found that they ranged to as low as — 72 mm. of mercury and were lowest for the cultures

TABLE 2.—*Results of Experiments D and E*

Experiment D

Date of inoculation: 10/12/31

During the two weeks before sealing, all of the cultures presented a fine granular growth evenly distributed over the surface of the potato medium

Date of sealing: 10/26/31

Oxygen, per Cent	Carbon Dioxide, per Cent	Nitrogen, per Cent	Growth After 53 Days*
75	0	25	#
65	0	35	#
23	1	76	+
22	2	76	+++
20	4	76	#
18	6	76	#
16	8	76	#
14	10	76	#
Control, evacuated, filled with air and sealed......................			+++
5 controls, unsealed..			++++

Experiment E

Two series of cultures were used. In one series growth was allowed to develop for eighteen days before sealing, in the other, the tubes were sealed on the day of inoculation. All tubes were sealed at the same time so that the same gas mixture could be used in corresponding tubes

		Series A	Series B
Date of inoculation........................		1/30/32	2/17/32
Sealed....................................		2/17/32	2/17/32
Oxygen, per Cent	Carbon Dioxide, per Cent	Growth After 6 Weeks*	Growth After 6 Weeks
100	0	+++	0
0	100	#	0
99	1	+++	+++
96	4	#	++++
95	5	++	++
94	6	Ceased growing	++
92	8	++	++
90	10	+++	+++
85	15	+++	++
80	20	+++	0
70	30	+++	0
50	50	#	0
25	75	#	0
Air....................................		+++	+++
Control.................................		++++	++++

* # indicates that the growth turned black and the bacilli had a granular appearance microscopically and failed to grow on subculture. The medium was not decolorized as it was by mature cultures. + indicates that growth continued, decolorizing the mediums, and yielded active growth after transplantation.

showing the most abundant growth. There was relatively little negative pressure in the tubes showing no growth. (No corrections were made for temperature, but the negative tensions were out of all proportion to the small differences of temperature at which we worked.) We therefore concluded that the capacity of even a 1 by 10 inch test tube was much too small to warrant any conclusive interpretation except in tubes which did not present even an initial growth.
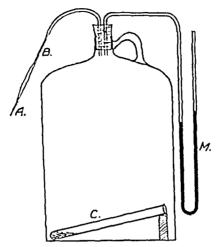
Fig. 3.—A gallon jar fitted with a mercury manometer (*M.*) and a sampling tube drawn out in two places (*A.* and *B.*). The Haldane sampling bottle is fitted by mercury-filled rubber tubing to *A.* By breaking *A.* within the tube, the sample could be taken, after which the sampling tube was sealed at *B.* Paraffined rubber stoppers proved to be an effective seal for these bottles. At the conclusion of the experiment another sample was taken in a similar manner at *B.*
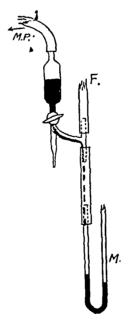
Fig. 4.—Method of sealing gallon jars with a mercury manometer (*M.*). The piece is attached (*F.* to *F.*) to the original apparatus.

We then planted small cultures in sealed gallon bottles (fig. 3). The bottles were fitted with mercury manometers and glass tubes from which samples of the gas could be drawn for analysis at the beginning and at the end of the experiment. The bottles were evacuated through the manometer tube, filled with the desired gas from the mixing chamber and sealed by dropping mercury into the manometer. To accomplish this the apparatus shown in figure 1 was modified by adding the piece shown in figure 4 and by supplying a 2 gallon mixing chamber using water as a displacement fluid. The results of this experiment are shown in table 3.

As an added experiment to show whether retarded growth in sealed tubes was due to accumulated carbon dioxide or to lack of oxygen, we devised the apparatus shown in figure 5. The bottle was filled with pure oxygen at a tension about 20 mm. greater than atmospheric pres-

TABLE 3.—*Results of Experiment F*

Date of inoculation: 1/27/32 Date of sealing: 1/27/32	One culture in a standard bacteriologic test tube was placed in each gallon jar	
Oxygen, per Cent	Carbon Dioxide, per Cent	Growth After 6 Weeks
100	0	0
95.7	4.3*	+++
62	33*	++++
Air.....		+++
Control.....		++++

* Analysis of a sample of gas from a bottle (Haldane apparatus). Gas was withdrawn from the bottles until the manometer columns showed the pressure in the bottles to be higher by 20 mm. of mercury than atmospheric pressure. There was no appreciable change from this reading in any of the bottles throughout the six weeks, eliminating the possibility of leakage.

sure. Cultures were planted and sealed on each end of the T tubes (the culture tubes initially containing air) so that from time to time, by giving the stopcocks a turn, an adequate supply of oxygen was assured. We assumed that under these circumstances the accumulated carbon dioxide would not escape into the bottle. This was verified by analyzing the gas in the bottle for carbon dioxide before and after the experiment. Cultures sealed with paraffined stoppers and open cultures were used as controls.

The growth in the experimental tubes and in the open tubes after six weeks was equal in amount and was designated by + + +, while that in the paraffined tubes was less in amount, being about ++.

In the course of the experiments we were greatly impressed by the aerobiosis of the tubercle bacillus. This has been commented on by others, but we feel that it is deserving of considerable emphasis. Particularly is this true for those who are using the cultural method as a diagnostic procedure. The capacity of the ordinary bacteriologic test tube is small. and the content being air. only a small amount of oxygen will be available. While not always successful. an attempt is usually

made to seal such tubes completely in order to prevent the medium
from drying out. In some tubes the sealing will be complete, and if
so the cultural conditions will be far from the best obtainable. We
have found the following alternative method simple and satisfactory:
A beaker or other receptacle is placed in a large-mouthed jar con-
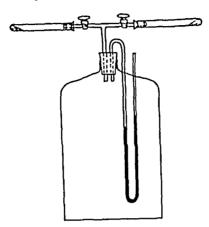
Fig. 5.—A gallon jar containing 100 per cent oxygen under slightly greater than
atmospheric tension. By a single turn of the stopcocks every one or two days,
any reduced tension (depleted oxygen) in the culture tubes was replaced with
oxygen.
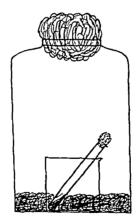
Fig. 6.—A large-mouthed jar with a cotton plug and cotton in the bottom kept
saturated with water. Culture tubes kept in such a jar may have free communica-
tion with air without danger of the medium becoming dry.

taining some cotton well saturated with water (fig. 6). A large cotton
stopper is used to plug the bottle. Under these conditions, cultures
on potato or glycerin agar when kept in the beaker need be stoppered
only with cotton. Many of our cultures were left open. An adequate
supply of oxygen is thus assured, and the medium has no tendency
to dry out as long as the cotton in the jar is moist.

CONCLUSIONS

1. In vitro experiments show conclusively that carbon dioxide in significant concentrations does not inhibit the growth of the human tubercle bacillus. On the contrary, a small amount is necessary for the beginning of growth. Concentrations such as are found in alveolar air or in venous blood seem to have a stimulating effect.

2. The tubercle bacillus will not grow in the absence of oxygen. Cultures grow considerably better when allowed free communication with air than when air-containing tubes are sealed, and a simple and satisfactory method of accomplishing this for the routine or diagnostic culture is suggested.

3. Therefore, so far as in vitro experiments indicate, increased carbon dioxide tension is not responsible for any beneficial effect that may be attributed to congestion.

4. The availability of oxygen is a highly significant factor in the growth of the tubercle bacillus.

INFLUENCE OF CONGESTION ON TUBERCULOSIS OF TISSUES OTHER THAN THE LUNG

Corper and Goldberg [16] reported that by constriction of the ear of a rabbit with a rubber band the carbon dioxide content of the plasma in the congested portion was increased from 10 to 20 and even 50 per cent. Following the intradermal injection of tubercle bacilli, the local development of tubercles was retarded, and ulceration with discharge of the contents occurred earlier than in the noncongested auricle of the same animal. There was no effect on the development of multiple metastatic lesions when bovine bacilli were used or on involvement of regional lymph nodes when human or bovine bacilli were used.

Levinson and Peterson [17] reported that there is no striking difference grossly between the passively congested liver of a rabbit and the liver of a control animal as to quantitative distribution or size of tubercles. Histologically, they found a greater deposit of fibrous tissue around and within the tubercles in the passively congested livers. Passive congestion was induced by injecting 0.5 cc. of liquid petrolatum intravenously twice a week for one month.

We feel that the problem of congestion and tuberculosis is important enough to justify more investigation. We do not feel that a marked degree of congestion was definitely enough demonstrated in Levinson and Peterson's rabbits. It should also be remembered that if the oil introduced into the blood stream plugs the capillary bed it will act as

16. Corper, H. J., and Goldberg, Max: Am. Rev. Tuberc. 8:567, 1924.
17. Levinson, S. A., and Peterson, W. F.:   Effect of Passive Hyperemia of the Liver on Tubercle Formation, J. A. M. A. **81**:723 (Sept. 1) 1923.

a foreign body and may itself be responsible for any variance in the tuberculous histologic picture, such as increased fibrosis. Particularly is this true since passive congestion per se is not productive of fibrous tissue.

For a study of the present problem to be in any way conclusive, two fundamental prerequisites must be satisfied: First, the tuberculosis in the controls must prove to be progressive, and second, the congestion of the organs should be as free as possible from complicating factors. In fulfilling the first postulate, our choice of experimental animals was limited. We made a special effort to apply our studies to the guinea-pig because of its definite and uniform susceptibility to human tubercle bacilli. We also attempted to use the lungs of the dogs, and our results with this animal will be given at a later date.

In fulfilling the second postulate, we produced chronic passive congestion by complete or partial venous ligation.

We would stress the first postulate, namely, that the tuberculous lesion must prove to be progressive in the controls. Much of the experimental work which has been done to test the influence on tuberculosis of possible therapeutic devices, whether biologic, chemical or mechanical, has been done by the intravenous injection of tubercle bacilli, and the appearance of tubercles in the treated tissue has been taken to negative any possible benefit of the therapeutic agent or device. It is known that emboli of tubercle bacilli, whether dead or alive, will produce a tuberculous histologic process wherever they lodge, and the process produced by dead bacilli is indistinguishable from that produced by viable bacilli. Of course, the lesion produced by dead bacilli will heal as soon as the toxins of the organisms have been spent. The lesion produced by living organisms may or may not progress. Therefore, we are not interested in, or rather we do not expect to find, a therapeutic agent which will prevent the appearance of a tuberculous histologic picture in the treated tissue. We are concerned chiefly with ascertaining any inhibiting effect of the agent on the progress of a tuberculous lesion when compared with a suitable control. Possibly this effect may be manifest only in the histologic characteristics rather than in the size of the lesion at any particular time in its development. It is important, therefore, to be acquainted not only with the characteristics of the normally developing lesion but with any criteria by which an inhibiting effect could be determined. In general, susceptibility is expressed by degeneration and caseation, the effects so outstanding in children and very susceptible adults, and resembles so markedly the process in monkeys that it has been referred to as "monkey tuberculosis." [18]

18. Fox, Herbert: Some Observations on the Development of Pulmonary Tuberculosis in Lower Animals as Compared and Contrasted with Similar Lesions in Man, Am. Rev. Tuberc. **17**:435, 1928.

Resistance is manifested by fibrosis and calcification. Theobald Smith[19] classified the evidences of tissue resistance in the following order: (1) giant cells; (2) giant cells with a mantle of epithelioid cells showing a tendency to sclerosis and without necrosis; (3) a more extensive process with caseation and calcification; (4) a group of tubercles due to unhindered bacillary growth, forming a large focus, and (5) a rapid
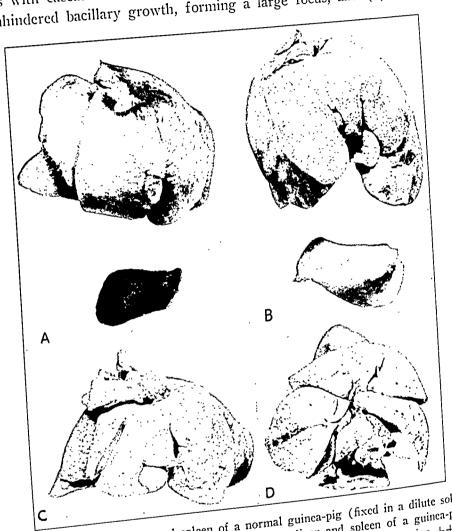
Fig. 7.—*A*, the liver and spleen of a normal guinea-pig (fixed in a dilute solution of formaldehyde, U. S. P. [1 : 10]). *B*, the liver and spleen of a guinea-pig that died fourteen days after complete ligation of the vena cava (congestion ++). The ligature can be seen beneath the diaphragm. *C*, the liver of a guinea-pig that died twenty-one days after complete ligation of the vena cava (congestion ++++). Regeneration of the liver is more evident than in *B*. *D*, cross-section of the liver which is shown in *C*, showing the evidence of cell regeneration and fatty degeneration. All the photographs were taken at an equal distance.

19. Smith, Theobald: Certain Aspects of Natural and Acquired Resistance to Tuberculosis and Their Bearing on Preventive Measures, J. A. M. A. **68:**704 (March 10) 1917.
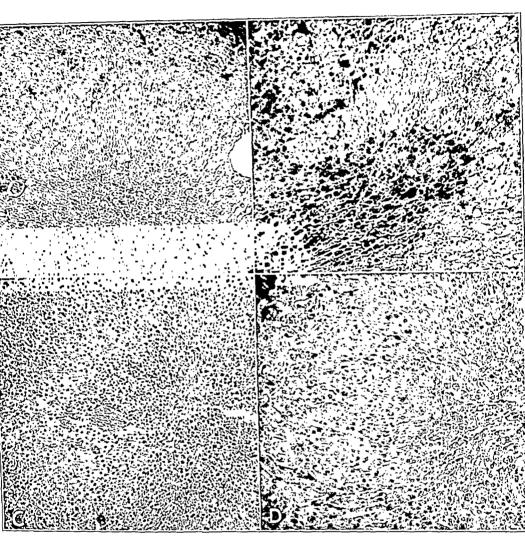
Fig. 8.—*A*, a low power photomicrograph of a section of the liver from a normal guinea-pig. A portal area can be seen on the left, and a central vein on the right. *B*, a section of a congested liver from a guinea-pig that died twenty-three days after complete ligation of the vena cava (congestion ++++). There are marked fatty degeneration and death of cells about the central veins. The viable cells are greatly swollen. *C*, an early tubercle in the liver of a control animal, showing death of the liver cells and the usual infiltration with mononuclear cells. The animal died twenty days after inoculation (tuberculosis +). Giant cells are occasionally seen in such early tubercles. *D*, an early tubercle in a liver congested for thirty days by partial ligation of the vena cava (tuberculosis +; congestion +++). The animal died twenty-four days after inoculation. All the photomicrographs were taken at the same power of magnification.
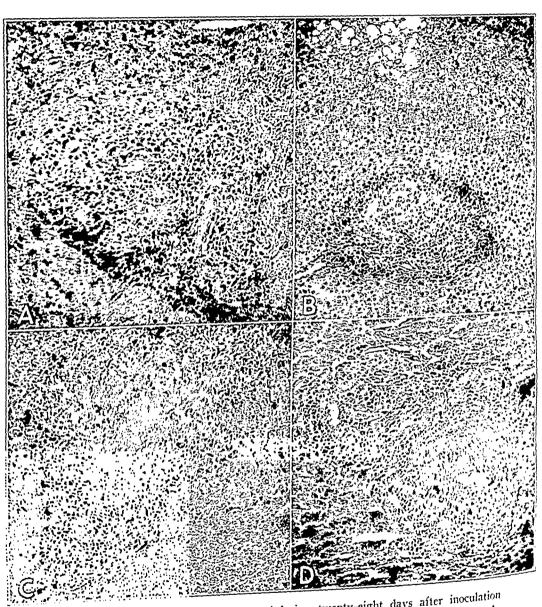
Fig. 9.—*A*, a moderately advanced lesion twenty-eight days after inoculation (tuberculosis +++). The lesion is in a periportal space. *B*, a moderately advanced tubercle twenty-eight days after inoculation in a liver congested for thirty-three days as a result of partial ligation of the vena cava (tuberculosis +++; congestion ++++). The lesion is in a periportal space and shows epithelioid cells. *C*, an advanced lesion in a control animal thirty-three days after inoculation, showing marked caseation (tuberculosis ++++). *D*, an advanced lesion thirty-three days after inoculation in a liver congested for thirty-eight days as a result of partial ligation of the vena cava (tuberculosis ++++; congestion +++).
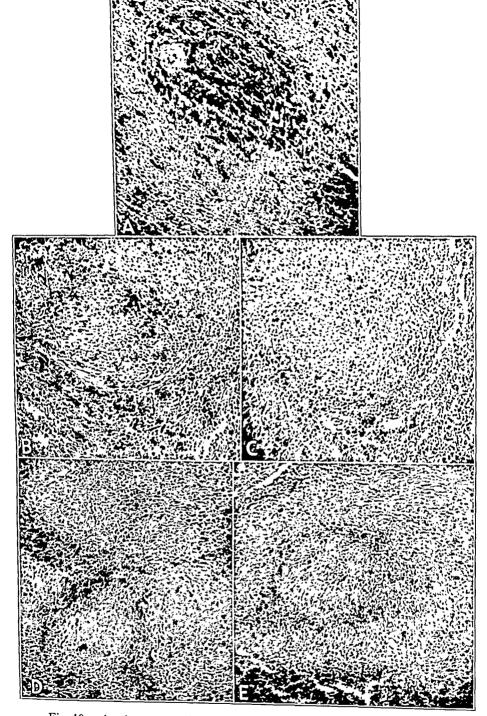
Fig. 10.—A, a low power photomicrograph of the spleen of a normal guinea-pig showing a malpighian corpuscle. B, a moderately advanced (+++) lesion in the spleen of a control animal twenty-eight days after inoculation. Caseation is present at this stage. C, a moderately advanced (+++) lesion twenty-four days after inoculation in a spleen congested for thirty days by partial ligation of the vena cava. D, an advanced (++++) lesion in a control animal thirty-three days after inoculation. The tubercles are conglomerate with caseation. Two giant cells are present. E, an advanced (++++) lesion twenty-eight days after inoculation in a spleen congested for thirty-three days by partial ligation of the vena cava.

multiplication of the bacilli within a focus with marked necrosis of tissue. It has been shown by Krause[20] that bacilli injected into the groin of a guinea-pig pass by way of the lymphatic system to the superficial and deep inguinal nodes and thence to the lymphatics about the common iliac artery and the abdominal aorta. They empty into the blood stream by way of the thoracic duct at the junction of the internal and the external jugular vein on the left side. The course then is to the lungs and through them to the peripheral organs. The spleen receives organisms entirely from the arterial blood stream, while the liver is supplied by the arterial and the portal stream, the latter coming from the intestinal tract and the spleen. The spleen and the liver are the most frequently and severely involved of the visceral organs, the spleen probably because it is rich in lymphoid tissue and the liver probably because it is fed by the spleen.

COMPLETE LIGATION OF THE INFERIOR VENA CAVA OF THE GUINEA-PIG

By Dr. Hyndman, Dr. Harry Landt, Dr. A. R. Anneberg
and Dr. J. D. Goldstein

Under ether anesthesia and with aseptic precautions a midline incision about 1 inch (2.5 cm.) long was made in the abdomen of the guinea-pig, beginning over the xiphoid process. By gently retracting the liver downward and cutting the thin falciform ligament, the portion of the inferior vena cava between the diaphragm and the liver was brought into view. By means of a ligature carrier a ligature of fine black silk was passed around the vein and the vessel was ligated completely. The peritoneum and the muscular layers and then the skin were closed with a continuous black silk suture. The operative mortality, either immediate or within two or three days, was 80 per cent. Five animals, however, lived from twelve to forty-five days, and the wounds were well healed. A few days following the operation the experimental animals and their controls received 2 minims (0.12 cc.) of a diluted suspension of tubercle bacilli (Gluckson strain) in the groin. The suspensions were made fresh each time from young subcultures by shaking with glass beads in sterile physiologic solution of sodium chloride. After we had obtained as fine a suspension as we could by this method the top suspension was diluted until the opalescence disappeared. The effect of complete or partial venous ligation on the liver was marked (fig. 7). Within two weeks the liver became enlarged and presented a marked nodular appearance. Though the engorgement of the spleen was usually evidenced by considerable swelling, this was not constant. The peritoneal cavity at the time of postmortem examination

20. Krause, A. K.: Am. Rev. Tuberc. 4:135, 1920.

presented a varying amount of ascites, the fluid usually being blood-tinged. The effect on only the liver and spleen was studied. Microscopic sections of these organs were taken and stained with hematoxylin

TABLE 4.—*Results of Experiment G*

Animal	Days Between Operation and Inoculation	Days Animal Lived After Inoculation	Pathologic Changes		
			Congestion of Liver*	Tuberculosis†	
				Of Liver	Of Spleen
1	5	12	+++	0	0
Control	..	15	..	0	0
2	5	16	++++	÷	++
Control	..	16	..	0	÷÷
3	4	19	++	÷	+
4	4	19	++++	÷	÷
Control	..	22	..	÷	++
5	7	45‡	+++	0	÷
Control	..	45‡	..	0	+

* The degree of congestion of the liver is represented by + to ++++, the latter being the maximum. The degree of congestion was determined microscopically, and this agreed closely with the gross appearance of the liver.
† The degree of tuberculosis is designated as follows: 0, no tuberculous histologic changes present in the sections examined; +, only one or two early lesions; ++++, advanced lesions with marked caseation (photomicrographs, figs. 8 to 10).
‡ These two animals were killed after forty-five days and showed marked involvement of the lymph nodes from the inguinal to the peribronchial nodes but no tubercles in the liver.

TABLE 5.—*Results of Experiment H*

Animal	Days Between Operation and Inoculation	Days Animal Lived After Inoculation	Suspension†	Pathologic Changes*		
				Degree of Congestion of Liver	Tuberculosis	
					Of Liver	Of Spleen
1	3	19	a	+	0	0
2	0	24	b	+++	0	+
3	6	24	b	+++	+	+
4	3	26	a	+	++	++
5	2	27	c	++++	0	+
6 (control)	..	27	c	..	++	++
7	0	31	a	++++	0	+
8 (control)	..	34	c	..	+	+++
9 (control)	..	34	a	..	+	++
10‡	0	35	a	++	0	0
11‡	0	35	a	+++	0	+
12	6	35	b	++	++	+++
13 (control)	..	38	b	..	÷+	+++
14 (control)	..	40	b	..	++	++
15‡	5	40	b	++	++	++
16	8	42	b	++++	++	++
17 (control)	..	43	b	..	+++	+++
18 (control)	..	43	b	..	+++	++++
19‡	5	44	b	++++	+++	+++
20	10	55	c	++++	+++	+++
21 (control)	..	55	c	..	+	++++

* The degree of congestion and of tuberculosis is indicated as in table 4.
† Three different suspensions (a, b and c) were used in this experiment and made fresh for each group inoculation. The letters represent animals which received 2 minims of the same suspension.
‡ These animals were killed; all the others died.

and eosin, and the lesions in the congested organs were compared with those in the control.[21] The results are given in table 4.

21. Dr. Hansmann and Dr. Schenken aided us in the interpretation of these sections.

In this experiment the development of tuberculosis seemed very slow in all the animals. One of the animals operated on and its control, which were killed after forty-five days, to our surprise showed no tuberculosis in the liver and very early lesions in the spleen, though the retroperitoneal glands were caseous. As we believed that the organism employed had become attenuated through numerous subcultures, we decided to study two series of animals with partially ligated veins, using the Gluckson strain in one series (experiment H, table 5) and a first culture of organisms obtained from a tuberculous epididymis in the other (experiment I, table 6).

TABLE 6.—*Results of Experiment I* *

Animal	Days Between Operation and Inoculation	Days Animal Lived After Inoculation	Pathologic Changes†		
			Degree of Congestion of Liver	Tuberculosis	
				Of Liver	Of Spleen
1............................	4	10	+++	0	0
2 (control)...................	..	20	..	+	++
3............................	3	23	++++	0	+
4............................	5	28	++	+++	+++
5‡...........................	5	28	++++	++	++
6 (control)...................	..	28	..	+++	+++
7............................	4	29	+++	++	+++
8 (control)‡.................	..	29	..	+++	++++
9 (control)...................	..	30	..	+	++
10 (control)..................	..	32	..	+	++
11‡..........................	5	33	+++	+++	+++
12 (control)‡.................	..	33	..	+++	+++
13 (control)..................	..	33	..	++	+++
14 (control)..................	..	34	..	+++	++++
15...........................	5	35	++	++	++
16 (control)..................	..	35	..	+++	+++
17...........................	4	45	++++	+	+
18...........................	3	45	++++	+++	+++

* All the animals in this series received 2 minims of the same suspension.
† The degree of congestion and of tuberculosis is indicated as in table 4.
‡ These animals were killed; all the others died.

PARTIAL LIGATION OF THE INFERIOR VENA CAVA OF THE GUINEA-PIG

In the experiments with partial ligation the operative technic was altered somewhat. It was found to be of considerable advantage to elevate the animal board about 60 degrees. In this position, the liver fell away from the diaphragm by gravity, eliminating the necessity of retraction or of manipulating the abdominal contents in any way. This advantage plus that of the partial ligation of the vena cava lowered our operative mortality from 80 to 20 per cent. The partial ligation was effected by incorporating a ligature carrier (1.5 mm. in diameter) in the ligature. When the hook was removed, a lumen in the vein 1.5 mm. in diameter remained. The size of the lumen was checked at all postmortem examinations. The evidences of congestion in the liver and spleen after this method seemed just as marked as after complete ligation.

COMMENT

In most of the animals the tuberculosis of the spleen appeared greater in amount and more advanced than that of the liver. It never appeared to be less extensive in the spleen.

It would seem as one examines the tables, particularly table 6 (experiment 1), that an occasional animal that lived a long time showed relatively less tuberculosis. No significance can be attached to this, however, in respect to the animals operated on, because the controls exhibited the same phenomenon. A possible explanation is that the guinea-pigs varied slightly in susceptibility to tuberculosis or that the dosage varied in spite of our attempt to standardize it.

In studying the sections from the animals showing more advanced changes the impression was obtained that the amount of tuberculosis in the animals operated on was definitely less than in the controls after a corresponding period. There was no difference, however, in the size or the histologic appearance of the individual lesions. On this basis it is our impression that the fewer lesions can be attributed to the retarded or congested circulation. Our interpretation of the findings is that congestion retarded the development of tuberculosis in respect to the gross number of lesions but that it had no effect on the growth and progress of the existing lesions, and the end-result was the same in all animals.

In the experiment made after partial ligation of the vena cava, the results did not differ for the two strains of tubercle bacilli.

CONCLUSIONS

Passive congestion produced by complete or partial ligation of the inferior vena cava of the guinea-pig has no influence on the progress or the histologic characteristics of tuberculosis in the liver and spleen produced by human tubercle bacilli.

The number of lesions is smaller in congested organs than in the corresponding organs in the controls, a fact which can probably be attributed to the retarded circulation.

SURFACE TEMPERATURE TEST IN VASCULAR OCCLUSION AND VASOMOTOR SPASM

ITS VALUE IN RELATION TO SYMPATHECTOMY

R. CUNLIFFE SHAW, M.Sc.

PRESTON, ENGLAND

The general assumption that the pathologic conditions which are amenable to treatment by sympathectomy are dependent on vasomotor spasm has led to the estimation of surface temperature as an index of the potential degree of vascular release. The skin temperature and the potential rise have been investigated by exposure to high environmental temperatures and by blockage of the vasomotor impulses by the injection of procaine hydrochloride into the peripheral nerves or by the use of spinal anesthesia.

From a study of these methods it has been found that, there is a gradation of the skin temperature from the trunk to the extremities in normal persons, which may be termed the vasomotor gradient, and that exposure of the body to a uniform warm air temperature of from 34 to 38 C. (93.2 to 100.4 F.) produces generalized vasodilatation with equalization of the temperatures of the central and distal surfaces. Coller and Maddock [1] have shown that in healthy persons exposure of the body to uniform high environmental temperatures results in a rise of skin temperature to an average level in men of from 34 to 35 C. (93.2 to 95 F.) and in women of from 35 to 36 C. (95 to 96.8 F.).

The application of similar tests of vasodepression in patients suffering from vascular diseases has been shown to result in a failure of the surface temperature to rise to the average levels attained in normal persons, and the difference between the maximum surface temperatures in the normal and in the pathologic cases is regarded as an index of the degree of vascular occlusion. As the result of their studies, Coller and Maddock divided the cases of vascular disease into three groups. In the first there is a slight change or no change following the application of tests of vasodepression. In this group they placed advanced cases of thrombo-angiitis obliterans and of peripheral arteritis. They regarded cases in this group as evidencing definite vascular occlusion and stated that sympathectomy is contraindicated. In the second group, in which there is a normal rise in surface temperature, taken as an indication of

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1. Coller, F. A., and Maddock, W. G.: Ann. Surg. 96:719 (Oct.) 1932.

the total absence of arterial block, they considered that sympathectomy offers the greatest possibility of relief. This group shows a combination of occlusion and vasospasticity.

The importance attached to the observation of a rise of surface temperature in the estimation of the prognosis and operability in cases in which sympathectomy is indicated suggested the study of the recovery period in such cases in relation to the surface thermal changes. The outcome of these observations and the detailed investigation of a case of vascular occlusion have shown that the foregoing conclusions must be modified.

Before discussing these results it should be noted that all sensitive methods for the estimation of surface temperature depend on thermoelectric principles, the pole or poles of the apparatus being applied to the skin or introduced into the dermal tissue, as practiced by Uffreduzzi,[2] and that the slight local variations are rapidly recorded by the galvanometer.

The details of a case of vascular occlusion are as follows:

REPORT OF CASE

A man, aged 59, noticed an ulcer on the fourth toe of the left foot about Easter, 1930. He thought that it was caused by the pressure of his clog. In August of the same year a constant aching and burning commenced, and the ulcer remained unhealed. In December the left foot became cyanosed and generally painful and was markedly swollen after walking. On Feb. 9, 1931, he was admitted to the hospital. There was complete gangrene of the terminal phalanx of the fourth toe, and the third toe was congested and showed two hemorrhagic blisters. The entire foot was slightly swollen and felt warmer than the right foot. The skin over the dorsum was cyanosed. The surface temperature readings, taken by the Campbell-Smith platinum resistance thermometer, are given in table 1.

Perifemoral sympathectomy was performed on February 24. There was no further change of surface temperature. The gangrene reached a stationary condition in the fourth and second digits, which were amputated on March 12. After a period in the hospital for convalescence he was discharged. He was free from pain; the amputation scar was healed, and the skin of the foot was a normal pink on exposure to warm air. In July, slight pain returned in the foot, which varied in severity throughout 1931 until June, 1932, when the foot again became swollen and the amputation scar of the second toe broke down, forming a small discharging ulcer.

The patient was readmitted to the hospital on October 2. There was a small hypersensitive ulcer on the plantar aspect of the base of the second toe. The foot was deeply cyanosed, but this condition disappeared on elevation. Apart from this, the skin over the remainder of the foot had a normal appearance. It was noticed that deep pressure in the popliteal fossa caused a rapid change in the tint of the skin, with almost immediate blanching of the blood vessels of the surface. This suggested that there was a marked degree of vasomotor spasm. The patient was accordingly tested for vascular release by exposure to high environment tempera-

2. Uffreduzzi, O.: Gaz. d. hôp. **101**:265, 1928.

tures under a radiant heat lamp. The average surface temperature over the feet under these conditions was from 35 to 36 C. (95 to 96.8 F.). A further estimation was carried out under spinal anesthesia, which resulted in a rise in the temperature of both legs of between 6 and 8 degrees C. (11 and 14 F.), a considerable rise for a man of this age and type.

On October 5 lumbar ganglionectomy was performed on the left side. The third and fourth ganglions and a portion of the second ganglion were excised, and the chain was divided below the fourth ganglion. After the operation the estimation of surface temperature showed an average rise of from 3 to 4 degrees C. (5 to 7 F.) over the affected foot. The color of the skin was normal, and on release of local pressure there was rapid filling of the surface vessels, indicating an active cutaneous circulation. Clinically, the operation was a complete failure. The pain increased in severity, and the discharge from the ulcer persisted.

In view of the severity of the pain, the popliteal nerves were exposed under procaine hydrochloride anesthesia, and an injection of a 30 per cent solution of antipyrine containing 2 per cent procaine hydrochloride was made. At the same time the popliteal artery was stripped, and an injection of absolute alcohol was made in its sheath in view of the possibility of inadequate ganglionectomy. It was

TABLE 1.—*Surface Temperature Readings in a Patient with Vascular Occlusion in the Lower Left Extremity (C.)*

	Middle of Dorsum	Ball of Great Toe	Middle of Heel	Anterior Middle of Leg	Posterior Middle of Leg	Patella	Anterior Middle of Thigh	Posterior Middle of Thigh
Left foot...	33	31.5	32.5	31.5	33.0	34	33	35.5
Right foot..	30	29.0	30.5	31.5	31.5	31	33	35.0

observed that there was no phase of contraction during this procedure, which had been marked at the primary perifemoral sympathectomy. Pain was relieved by these methods for only twelve hours, and there was no further rise in surface temperature.

On November 3 the leg was amputated on account of the intolerable pain. Up to this time the only surface lesion was the small discharging ulcer at the distal end of the plantar surface. The changes in surface temperature were maintained to the time of amputation.

Immediately after the amputation I injected iodized poppy-seed oil 40 per cent into the anterior and posterior tibial arteries and took roentgenograms of the foot. These showed that the anterior tibial artery was blocked at about the level of the anterior annular ligament and that the posterior tibial artery was obstructed near its bifurcation into the external and internal plantar arteries. The blood supply of the foot was carried on by the peroneal and malleolar vessels, and the roentgenogram showed a free injection of the vessels of the surface around the heel, although the iodized oil had not penetrated into the vessels of the more distal surfaces.

The arteries were dissected, and the organic occlusion was found to correspond with the roentgenologic appearance. It was noted that the dermal structures over the entire foot, with the exception of the ulcerated area, were well supplied with blood. On the other hand, all the structures between the plantar fascia and the arch of the tarsus were completely necrotic, consisting of a pulpacious mass slowly liquefying and discharging through the peripheral ulcer.

In the case described there is definite evidence of two factors operative on the vascular system: (1) endarteritis, causing a complete blockage of the main peripheral arteries, and (2) generalized freedom of the

Roentgenograms of the foot taken after amputation, showing blocking of the anterior tibial artery and obstruction of the posterior artery: *A*, anterior view; *B*, lateral view, showing in addition congestion of the vessels of the surface around the heel.

dermal blood vessels from vascular occlusion, but a marked degree of vasospasticity prior to sympathectomy. The result of the first factor was slow aseptic gangrene of the subfascial plantar tissues, accom-

panied by intense irritation of the common sensory nerves. The second factor produced preoperative variations in the tint of the skin and a normal thermal response to high environmental temperatures, together with a maximal vascular release under spinal anesthesia, and absence of the occlusive index and good filling of the surface on the release of pressure.

It is evident that the sensitivity of thermo-electrical methods of determining changes in surface temperature gives results that are dependent on the response of the blood vessels of the surface. The

TABLE 2.—*Average Rise in Surface Temperature Compared with Time Required for Healing and Recovery Following Ganglionectomy and Periarterial Sympathectomy*

Case	Operation	Average Post-operative Rise in Temperature (Degrees, C.)	Period of Healing of Lesion	Period of Subsidence of Pain	Period of Freedom from Recurrence
1	Cervical ganglion-ectomy, left	0 to 1	Gangrene of index finger, 2-3 weeks	24 hours	21 months
2	Lumbar ganglion-ectomy, right	0.75 to 1.25	Deep plantar ulcer; healed, 2 weeks; filled, 6 weeks	Immediate	8 months
3	Lumbar ganglion-ectomy, right	2	Deep plantar ulcer; healed, 1 week; filled, 5 weeks	Immediate	7 months
4	Lumbar ganglion-ectomy, left	6	Pain crisis	Immediate	26 months
5	Periarterial sympathectomy	0.5 to 1; none after 3 weeks	Gangrene of term-inal phalanx, of second toe, 2-3 weeks	7 to 10 days	24 months
6	Periarterial sympathectomy	0.5; none after 2 weeks	Gangrene of term-inal phalanx of fourth toe, 3-4 weeks	Immediate	6 months
7	Periarterial sympathectomy	0.5 to 1; none after 10 days	Chronic ulcer of leg, 8 weeks	24 hours	24 months
8	Periarterial sympathectomy	0.5 to 1; none after 3-4 weeks	Chronic ulcer of leg, 16 days	24-48 hours	18 months
9	Periarterial sympathectomy	0.5; none after 12 days	Ununited fracture of tibia, 3-4 weeks, with excessive callus		

estimation of the rise in skin temperature in occlusive vascular disease as a criterion of operability introduces a factor of possible error. Thrombo-angiitis obliterans attacks first the principal distal arteries, which become obstructed long before the dermal vessels; hence the application of the temperature tests may lead to deductions based on vascular release of the dermal vessels in the presence of completely occluded deep arteries. On the other hand, the investigation of the potential vascular release based on the rise of dermal temperature must obviously be a reliable and valuable procedure in judging operability in cases of vasospasticity, and in this particular sphere I agree with the observations of Coller and Maddock that the more satisfactory method of estimating these changes is by the use of the high environmental temperature tests. The unpleasant psychic effects of peripheral nerve block and spinal

anesthesia make the employment of these tests objectionable to some patients, and, further, a fall in blood pressure and a correspondingly inadequate thermal response frequently follow their use.

The subject may be studied from another aspect. In table 2 I have indicated the average rise in surface temperature after ganglionectomy and periarterial sympathectomy in nine cases, the clinical results of which were classed as good. The relative time for recovery from the symptoms and for the healing of the peripheral lesion is compared with the rise in surface temperature and the period during which the hyperthermia was maintained.

TABLE 3.—*Average Rise in Temperature in Eleven Cases of Sympathectomy for Vascular Occlusion Recorded by Telford and Stopford*

Analysis of results		Number
Good		8
Fair		2
Failure		1
Total		11
Average rise in the temperature of the skin		**Degrees, C.**
Good results	Right and left sides	2.47
Fair results	Right and left sides	2.27
Good results	Right side only	2.243
Good results	Left side only	2.675
Fair results	Right side only	2.55
Fair results	Left side only	2
Average rise in the temperature of the skin in the limb which exhibited the more serious lesion		
Good results		1.725
Average rise in the temperature of the skin in nine cases of sympathectomy for miscellaneous conditions the results of which are classed as good (own cases)		
Average of highest temperatures...........................(approximately)		1.58
Average of lowest temperatures.............................(approximately)		1.39

It will be observed that in the cases in which the rise in temperature was of a minor degree, there was progressive healing of the distal lesion and cessation of pain, and that in several cases periarterial sympathectomy gave complete relief within from one to two years. These results form a striking contrast to the hyperthermia observed in the case already discussed. Moreover, another point may be noted from table 2: In several cases the comparatively small degree of hyperthermia ceased long before the healing of the surface lesion.

In table 3 I have set down the average rise in surface temperature in a series of cases which were reported by Telford and Stopford.[3] It will be seen that, taking the average rise of temperature in the cases in which the results were classed as good in the affected limb which showed the more serious clinical symptoms, the average hyperthermia

3. Telford, E., and Stopford, J. S. B.: Brit. M. J. **1**:1116 (June 18) 1932; ibid. **1**:173 (Feb. 4) 1933.

was less than that in the cases in which the clinical results were classed as fair. This compares favorably with the average hyperthermia observed in the nine cases classed as good in my own series.

These facts suggest that, although vascular dilatation must play some part in the healing of peripheral lesions, it is by no means the sole factor. There is evidence to show that sympathectomy may directly alter the physiochemical balance of the tissue cells, and that slight changes of the hydrogen ion concentration may occur after this procedure.

Jung and Leriche described reactions in sympathectomy wounds varying from acid to alkaline, whereas in wounds that had not been subjected to sympathectomy the reaction was always acid. In this association the work of Fischer [1] has demonstrated the remarkable sensitivity of fibroblasts to the slight changes in the hydrogen ion concentration, and Balint and Weiss [2] have shown the striking effect of variation of the p_H of the tissue fluids on healing wounds. It is possible that some such change occurs at the margin of the tissue cells after sympathectomy and that this change of the ion concentration determines the nature of the inflammatory reaction, the destructive phase giving place to the assimilative one.

CONCLUSIONS

It is concluded that the estimation of the potential rise in surface temperature is a useful index of the degree of vasospasticity of the dermal blood vessels and can be applied particularly in pure vasomotor conditions, such as Raynaud's disease. On the other hand, the application of these tests in cases of occlusive vascular disease, such as thrombo-angiitis obliterans, is of very slight value for the following reasons: first, on account of the factor of possible error; second, because considerable hyperthermia is not necessary for the relief of the symptoms or the healing of the peripheral lesions, and third, because although these cases exhibit varying degrees of vasospasticity of the surface blood vessels ganglionectomy is by no means able to overcome the effects of a complete block of the deeper vessels (as shown in the case reported in this article), and it is suggested that some change other than mere vasodilatation may be necessary for a successful result from sympathectomy.

4. Fischer, A.: J. Exper. Med. **34**:447, 1921.

5. Balint, R., and Weiss, S.: Tissue Proliferation and Acid Base Equilibrium, translated by F. Morena and G. C. Pether, London, Constable & Co., Ltd., 1932.

OBSTRUCTIVE JAUNDICE

DUE TO DIFFUSE CONTRACTURE OF THE EXTRAHEPATIC BILE DUCTS

HENRY K. RANSOM, M.D.
AND
KARL D. MALCOLM, M.D.
ANN ARBOR, MICH.

The problem of benign stricture of the bile ducts is one which in recent years has come to occupy a position of major importance in the field of abdominal surgery, as is attested by the numerous papers on the subject which may be found in the current literature. While a few decades ago clinical observations and case reports were concerned chiefly with the so-called congenital strictures which are of interest to the pathologist but usually surgically hopeless, today the acquired type of stricture assumes the predominant rôle. The reasons for this are: first, the greater frequency with which these acquired strictures are encountered, probably owing to the more widespread practice of cholecystectomy; second, the chance of affording relief by surgical therapy now possible with the development of appropriate operative procedures for dealing with such lesions, and third, the importance of their prevention.

For the most part the congenital strictures do not concern the surgeon. This condition is characterized by complete biliary obstruction appearing a short time after birth, and it ordinarily soon leads to a fatal termination. The situation of the obstruction and the type of lesion may show the utmost variation in different cases, but obliteration of the lower end of the common bile duct or complete occlusion of the whole duct seems to be found most often, while abnormalities of the hepatic duct are perhaps second in frequency. The pancreatic duct is only rarely affected. Along with these changes in the major ducts, obliteration of the cystic duct or even absence of the gallbladder is a frequent accompaniment. Occasionally a patient with a congenital stricture of the common duct may survive until adult life; interesting cases have been reported by Treves,[1] Mathieu [2] and Judd and Burden.[3] While

1. Treves, F.: A Case of Jaundice of 16 Years' Standing Treated by Operation, Practitioner 62:18 (Jan.) 1899.

2. Mathieu, Paul: Retrécissements non néoplasiques des voies biliares principales, Rev. de chir. 37:61, 1908.

3. Judd, E. S., and Burden, V. G.: Benign Stricture of the Bile Ducts, Arch. Surg. 11:459 (Sept.) 1925.

the nature of the pathologic process of these strictures is not clearly understood, it has been suggested by Moynihan[4] and Rolleston[5] that during fetal life, poisons developed in the body of the mother are carried to the liver of the fetus, provoking a combination of cirrhosis and cholangeitis, the end-result being an obliterative cicatrization of the ducts. Some doubt may be cast on this view by the observations of Feldman and Lawson[6] in 1924 who noted the presence of congenital stricture in one of a pair of binovular twins, the fellow twin being quite normal. Other authors, notably Rolleston,[7] have reported cases of congenital stricture of the common duct which they believed were caused by syphilis.

The second group, or the acquired type of stricture, is the one in which we are chiefly interested. Here we have more positive information regarding etiology, and considerable clinical experience has accumulated concerning operative treatment. The acquired strictures may be subdivided into a traumatic and an inflammatory group. Of the traumatic type, by far the greatest number of instances are those in which injury to the hepatic or common duct during cholecystectomy has occurred. This injury may consist in an actual severing or ligation of the duct or even excision of a segment; wounding of the duct with the production of an external biliary fistula and subsequent cicatrization; or perhaps most commonly, the placement of the ligature of the cystic duct too close to the common duct so as to compromise its lumen when the ligature is tied. In other instances, it has been suggested that an abnormal amount of scar tissue may develop about the duct from the use of too large or too heavy gauze drains, with the ends left close to the duct. Again, damage to the circulation of the duct from an overzealous denudation at the time of operation has been mentioned. These strictures naturally are usually located near the junction of the cystic and hepatic ducts and are fairly circumscribed; frequently there is a segment of normal duct above and below the point of obstruction, a fortunate finding when surgical reconstruction of the duct is to be done.

The inflammatory variety of acquired stricture is commonly regarded as due to a localized cicatrix presumably caused by an initial ulceration of the mucous membrane by the passage of a gallstone or to impaction of a stone in the wall of the duct with resultant injury and subsequent

4. Moynihan, quoted by Judd.[3]

5. Rolleston, H. G.: Diseases of the Liver, Gall Bladder and Bile Ducts, London, The Macmillan Company, 1912.

6. Feldman, William, and Lawson, M. A.: A Case of "Congenital" Occlusion of the Common Hepatic Duct in a Twin Baby, with an Indirect van den Bergh Reaction, Lancet **2**:113 (July 19) 1924.

7. Rolleston, H. G.: Congenital Syphilitic Obstruction of the Common Bile Duct, Brit. M. J. **2**:947, 1907.

contraction of the scar tissue during the healing process. Such strictures are usually quite localized and found in a duct which at other points is within normal limits.

According to Judd [8] these etiologic factors of initial injury have been greatly overrated, and he believes that in many of these so-called acquired inflammatory and traumatic strictures, the process is fundamentally an obliterative cholangeitis. In support of his contention he cited cases in which the clinical evidence of stricture did not appear until many months or even years after the cholecystectomy.

Finally, there is another and fortunately more unusual variety of obstruction of the common duct, namely, the diffuse fibrosis of the entire system of extrahepatic ducts with ultimate contracture whereby the ducts are converted into a small thick-walled tube with severe compression or even occlusion of the lumen. This type of lesion in all probability should be regarded as an obliterative cholangeitis, since the factors of previous operations or preexisting gallstones can be excluded in the majority of the reported cases. As an example of this type, we relate the history of such a case in which the patient was only recently under our care.

REPORT OF CASE

CASE 1.—*History.*—O. P., an American tanner, aged 35. was admitted on Oct. 12, 1932, with a complaint of "stone in the common duct."

His health had been good until seven weeks prior to admission to the hospital, at which time he first experienced an attack of rather severe acute abdominal pain, which was colicky and localized to the right upper quadrant of the abdomen. The pain did not radiate. This first attack lasted for several hours, and slight nausea and vomiting were associated with the pain. The symptoms continued with less severity and he was required to give up his work and go to bed. The daily nausea and vomiting continued until one week before admission. The vomitus was greenish and occasionally it was streaked with blood. He had had no chills or fever as far as he was aware. Three weeks before admission, jaundice was noted for the first time. Along with this the patient noticed that the urine was dark, but he did not know whether the stools had been clay colored. The pain in the right upper quadrant came on two or three times a day, remaining quite well localized and being definitely colicky. It seemed to be aggravated by exercise, but had not progressed in severity. At the beginning of his illness he was seen by a local physician who told him that he had a stone in the common duct. His appetite had been poor since the onset of the trouble. He estimated that he had lost about 30 pounds (13.6 Kg.) during the seven weeks of his illness. His health had always been exceptionally good in the past. There had been no injuries or surgical operations. He was a moderate user of tobacco, but not of alcohol.

Examination.—The patient was a well developed and well nourished adult who appeared to have lost considerable weight and who was quite dehydrated at the time of admission. The skin and sclerae showed deep jaundice, and there were a

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8. Judd, E. Starr: Stricture of the Common Bile Duct, Ann. Surg. **84**:404 . (Sept.) 1926.

number of excoriations from scratching owing to the intense pruritus. The teeth were in poor condition, with marked oral sepsis. The tonsils were hypertrophic and septic. Otherwise, the head, neck and thorax were normal.

The panniculus was abundant, the anterior abdominal wall being slightly above the level of the costal margin. There was slight generalized tenderness, but otherwise the abdominal examination gave negative results. The gallbladder was not palpable.

The temperature, pulse and respiration were normal on admission and remained essentially so during the first few days in the hospital, with a slight rise in temperature to 99 or 100 F. in the afternoon.

Laboratory Examinations.—The Kahn test was negative. Examination of the blood showed a hemoglobin content of 59 per cent and a white cell count of 6,400. The bleeding time was four and a half minutes and clotting time eight minutes. The urine was normal except for the presence of bile in several specimens examined. The stools were clay colored. The blood bilirubin was 75 mg. per thousand cubic centimeters (direct van den Bergh test). A gastro-intestinal roentgen examination was made which revealed no organic disturbance in the upper portion of the alimentary tract. On account of the obstructive jaundice, cholecystograms were not made.

Preoperative Treatment.—The patient was given an abundance of fluids, a diet high in carbohydrate with calcium and dextrose administered intravenously over a period of eight days. The itching was considerably relieved by antipruritic treatment.

Comment.—This was a case of a healthy young man with a fairly short history of what seemed to be gallstone colic with jaundice developing subsequently, which suggested the likelihood of a stone in the common duct. It might be noted, however, that the jaundice had not been intermittent, but had continued without remission during the three weeks since it had first appeared. Although chills were not present there was a slight rise in temperature in the afternoon. The possibility of a pancreatic neoplasm was considered, but this was not regarded as very probable.

Operation (by H. K. R.).—On Oct. 20, under avertin, nitrous oxide and oxygen anesthesia, an upper right rectus incision was made. All tissues were found to be deeply jaundiced. The liver was normal in size, but blackish, suggesting biliary obstruction of fairly long standing. The wall of the gallbladder was thickened and the gallbladder was contracted, but it did not contain stones. The foramen of Winslow was patent, but exact identification of the common and cystic ducts was difficult, owing to an inflammatory process about the ducts. There was no evidence of dilatation of the common or hepatic ducts, and no stones could be felt on palpation. Attempts to aspirate the common duct were unsuccessful; therefore, in order to be very certain of the point of junction of the cystic and common duct, the gallbladder was dissected off of the liver and followed as a guide to the common duct. At a point just distal to the junction of the cystic and common ducts, by means of a very fine hypodermic needle, a drop or two of bile could be obtained. Following this, the duct was opened in a longitudinal direction. This was a difficult procedure because, as the incision was made, it was found that the common duct was so contracted as to be only a small fibrous cord with a thick, tough wall and

almost complete obliteration of the lumen. When the lumen was opened, a minute quantity of bile escaped. Probing of the duct could be done with nothing larger than a fine silver wire probe. This could be passed downward into the duodenum and upward into the hepatic ducts without encountering any definite point of complete obstruction. A uterine sound or the smallest bougie could not be introduced on account of the small size of the lumen. At this point an unfortunate happening occurred. Owing to the tension on this very slender fibrous duct in the attempt to probe it, the duct snapped completely in two at the point at which it had been opened. Because of the extreme narrowing of the lumen of the duct, it was impossible to reconstruct it over a T-tube or any small tube, as none was of sufficiently small caliber to be introduced. Likewise no catheter was small enough to permit its introduction into the cut end of the upper segment for the purpose of external drainage. As the operation had been somewhat prolonged, owing to this accident, and since the patient's condition was failing, in desperation the lower end of the duct was closed and the upper end brought up through the peritoneum, and the gallbladder necessarily removed. This part of the abdomen was then quarantined by the Coffey method of drainage and the abdomen was closed. Immediately a transfusion of blood was given and dextrose was administered intravenously continuously thereafter. His condition during the afternoon was poor, and at 6 o'clock a second transfusion of blood was given, but he rapidly became worse and died at 8:30 p. m.

Pathologic Report.—The report on the specimen removed (gallbladder) at operation was: "Chronic cholecystitis with diffuse fibrosis of the gallbladder wall. No stones were present. A lymph node included in the material showed chronic lymphadenitis of the sinus epithelium."

Necropsy.—A postmortem examination showed that the entire system of extrahepatic ducts had undergone extensive fibrosis with extreme narrowing of the lumen. The process included the common duct, the common hepatic duct and both right and left hepatic ducts to almost the same degree, with possibly more extensive alteration in the hepatic ducts than in the common duct. The liver showed a biliary cirrhosis. No other changes of importance were revealed. Death was undoubtedly due to shock from the prolonged operation in a patient who was a poor risk.

The unusual findings at operation called to mind an earlier operative experience in a somewhat similar case encountered about nine years before, a detailed account of which will be given (case 2). It also stimulated us to undertake a survey of the literature on the subject of stricture of the bile ducts, as at operation a condition had been discovered which was wholly unexpected and one in which the likelihood of cure by surgical intervention seemed highly improbable. We shall endeavor to give a short account of the more important recorded observations.

CASES IN THE LITERATURE

In 1927 Miller [9] reported a case very similar to ours in all particulars. Miller's patient was a man, 40 years of age, who presented himself with a history of recurrent attacks of severe pain in the upper part of the abdomen of five months' dura-

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9. Miller, Robert T., Jr.: Benign Stricture of Bile Ducts, Ann. Surg. **86**:296 (Aug.) 1927.

tion, these attacks usually being preceded by abdominal distress and associated with nausea and vomiting, finally terminating in a period of malaise lasting for two or three days. Symptoms of indigestion had become increasingly more severe. There had been a loss of 15 pounds (6.8 Kg.) caused by jaundice, which had developed three weeks before admission. The examination showed a well nourished man with moderate jaundice, slight enlargement of the liver, but without tenderness, muscle spasm or palpable masses in the abdomen. While the patient was in the hospital the temperature varied from 97.6 to 99.2 F. and the leukocyte count was normal. The gastro-intestinal tract was found to be normal on roentgen examination, and a roentgenogram of the gallbladder was negative for stones. The urine showed a positive reaction for bile, and the stools were clay colored, chemical tests showing only a small quantity of bile. The guaiac test was negative. The condition was thought to be a stone in the common duct, while the possibility of neoplasm was considered. At operation a chronically inflamed gallbladder was found without stones. Palpation of the common duct suggested a superficial saphenous vein occluded by organized clots. The whole duct was felt as a hard cord of slightly less than normal size. "The duct was opened, its wall was found to be greatly thickened throughout, its lumen much diminished in size and lying in it were a few flakes of deep colored soft débris. No bile came from the duct until a probe had been somewhat forcibly inserted into the hepatic duct, whereupon a small amount of very faintly colored secretion appeared. It was impossible to pass anything larger than a very fine probe into the duodenum, the lumen of the duct being all but occluded by its thickened wall. The exact nature of the change in the wall of the duct was not understood but because of bothersome bleeding no specimen was excised for diagnosis." The duct was closed and a cholecystogastrostomy done. The patient recovered from the operation, and all of his symptoms were relieved.

Pierre Delbet [10] in 1924 reported another almost identical case. His patient, a man of 48 years, complained of recurrent attacks of epigastric pain with nausea and vomiting of two years' duration, while jaundice had appeared ten days before the examination. Examination revealed extreme epigastric tenderness and muscle spasm. The stools were light colored. A diagnosis of stone in the common duct was made and a laparotomy performed; at this time a thin-walled gallbladder was found which was moderately tense and buried in light adhesions. The common duct was contracted, and on being incised it was found to have extremely thick walls with a very small lumen, although a fine catheter could be passed through the lower end of the duct into the duodenum. The catheter could not be passed to the liver, but evidently the duct was not completely occluded. The operation was therefore concluded by anastomosing the gallbladder to the duodenum. Convalescence was uneventful, and the jaundice disappeared.

Lafourcade [11] in 1925 reported the case of a man, 58 years old, who had had attacks of gallstone colic for thirty years. Jaundice had gradually developed eight months before admission. Examination showed the liver to be slightly enlarged, and the stools were clay colored, while the urine contained bile. A diagnosis of stone in the common duct was made and an operation performed. At this time the gallbladder was found to be contracted and buried in adhesions. The common duct

10. Delbet, Pierre: *Bull. et mém. Soc. nat. de chir.* **50**:1144, 1924.
11. Lafourcade, L.: *Bull. et mém. Soc. nat. de chir.* **51**:828, 1925.

was extremely indurated throughout its course, and when opened the wall was found much thickened, owing to general fibrosis. Lafourcade stated that the wall of the duct was 0.5 cm. in thickness and the lumen so small that only with the greatest difficulty could a stilet be inserted. In this case, the hepatic duct was apparently not very abnormal, for Lafourcade cut it across and inserted a rubber tube, the distal end of which was carried into the duodenum. The patient died forty-eight hours later, but permission for autopsy was not granted.

Dr. Allen O. Whipple,[12] of New York, discussed the case of a woman, aged 50, with pernicous anemia who came to him with a history of digestive symptoms and jaundice. The jaundice had been complete for two months before operation. At operation the gallbladder was found to be collapsed, the common duct was felt as a thickened cord throughout its entire length, including the common hepatic duct, and no bulging of the right or left hepatic duct could be made out. Because of the inability to locate a dilated duct, no attempt was made to drain either the gallbladder or the duct system. The liver showed an extensive cirrhosis of the biliary type which was proved by microscopic section. The wound was closed without further procedure and on the ninth day after the operation the patient began to show some bile in the stools and continued to recover without interruption. She remained well as far as was known.

These cases of Miller, Delbet, and Whipple seem to have been quite similar to case 1 in that the hepatic duct as well as the common duct was involved in the inflammatory process, while the case reported by Lafourcade differed slightly in that the hepatic duct did not show notable change. In considering the etiology of this condition, the striking thing about all of these cases is the absence of any previous abdominal operations and also the absence of stones in both the gallbladder and the ducts at the time of operation. The factor of operative trauma can be excluded, while damage to the ducts from the passage of stones at an earlier date seems highly improbable. Likewise the diffuse and uniform character of the process seems quite incompatible with such a causative agent. We are left, then, with the alternative of explaining the process on the basis of an obliterative cholangeitis which had led to ultimate diffuse fibrosis and contracture. This view seems to be substantiated in our case in which microscopic examination of the duct was possible, as the histologic examination showed a marked fibrosis of the walls of the ducts indicating a chronic cholangeitis with the process still showing some degree of activity (fig. 1). It is usual in infections of the biliary tract for the process to gain a foothold and produce the greatest damage in the wall of the gallbladder itself, while the ducts show a rather remarkable ability to resist infection. It would seem that in these rare cases, the gallbladder and the ducts shared alike in the inflam-

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12. Whipple, Allen O.:   Tr. Am. S. A. **45**:143, 1927.

Fig. 1 (case 1).—*A*, fibrosis of the hepatic duct; *B*, the same process in the common duct; × 80.

matory process and that even before stones have had a chance to form in the gallbladder, the maximum damage has been produced in the wall of the extrahepatic ducts, while the inflammatory process in the wall of the gallbladder has progressed to a lesser degree. We now present the report of the second case, to which reference has been made.

CASE 2.—*History.*—Mrs. N. G., a housewife, 53 years old, was admitted to the hospital on March 3, 1924, complaining of attacks of abdominal pain, gas and jaundice. She had never been very strong and had had all of the usual contagious diseases and frequent attacks of infections of the upper respiratory tract. Three years before, she contracted typhoid fever. The attacks of gas, flatulence and epigastric pain began about four years before admission. The pain tended to be more severe at night. In May, 1923, a cholecystectomy for gallstones was done. Since then she had never felt entirely well. There had been attacks of pain, gas and jaundice with chills and fever. The temperature frequently reached 104 F. Jaundice developed four weeks prior to admission.

Physical Examination.—The patient was a nervous slender woman of medium stature. The skin and sclerae showed marked jaundice. Abdominal examination revealed the scar of a former right rectus incision which was well healed but showed a slight tendency to keloid formation. There were no palpable masses and no muscle spasm.

Laboratory Examination.—Urinalysis gave negative results except for the presence of bile. The hemoglobin was 80 per cent, the red cell count, 4,156,000 and the white cell count, 7,300. The stools were clay colored. Examination revealed: no free fat; free starch, 1 plus; few undigested meat fibers; no ova. The coagulation time by the Howell method was twenty minutes.

Comment.—This was a patient with all the signs and symptoms of obstruction of the common duct developing nearly a year after cholecystectomy. On account of the pain and digestive disturbances along with the jaundice, chills and fever, a diagnosis of a stone in the common duct was made and operation recommended.

Operation (by Dr. F. A. Coller).—On March 4, under ethylene and oxygen anesthesia, a laparotomy was performed, the incision being made through the old scar. Adhesions were found between the liver and the parietal peritoneum and between the duodenum and transverse colon and the anterior aspect of the liver. The foramen of Winslow was open and an excellent exposure obtained. The common duct was found to be very small throughout its entire extent. It was impossible to pass a no. 8 F. bougie along its course. The duodenum was opened and an attempt made to secure some degree of dilation from this end, but it was impossible to pass even the smallest bougie into the common duct. The pancreatic duct was apparently somewhat dilated, as it could be probed throughout its entire extent with a no. 10 F. bougie. Absolutely no dilatation of the common duct existed up to the point where it went into the liver. There were enlarged glands along the course of the common duct, varying from 1 to 2 cm. in diameter. There was absolutely no evidence of any stone, and none could have been present as the examination was entirely adequate. The liver was enlarged, firm and extended three

fingerbreadths below the costal margin. Throughout the right lobe there were areas of increased density which seemed characteristic of isolated areas of cirrhosis. No other abnormalities were found. The duodenum was then closed and the abdominal wall closed in layers about a drain. As a prophylactic measure the patient was given a transfusion of whole blood following the operation although her condition at the time was excellent.

Comment.—At operation, instead of finding dilatation of the common duct as had been expected, quite the reverse was found. The common duct was markedly contracted into a very narrow fibrous tube with enlarged lymph glands along its course. Probing of the duct both from its lower end through the duodenum and through a choledochotomy incision revealed an extremely small lumen with great thickening and contracture of the duct walls. The process was uniform throughout the course of the hepatic and common ducts without stone and without stricture. In the absence of the gallbladder cholecystenterostomy was out of the question, and without dilatation of the hepatic ducts hepatico-duodenostomy was likewise impossible.

Postoperative Course.—On March 5 and 6 the patient's condition was entirely satisfactory. On March 7 abdominal distention began to develop along with nausea and vomiting. At midnight on March 7 the pulse rate had gone up to 140 and the temperature down to 97 F. She was uncomfortable and weak and the following morning was worse. In spite of all treatment, the abdominal distention persisted; she rapidly failed and died at noon on March 8.

Necropsy.—The postmortem examination performed on the day of death disclosed: an acute generalized fibrinopurulent peritonitis with intraperitoneal hemorrhage; chronic ascending cholangeitis with periportal cirrhosis; chronic obstructive jaundice; chronic infection of the common and hepatic ducts; hemorrhagic fat necrosis.

Death was evidently due to postoperative intra-abdominal hemorrhage, easily accounted for on the basis of the chronic jaundice, and peritonitis. The striking finding, however, was the uniform fibrosis and contracture of the hepatic and common ducts without stones and without stricture. Since a complete postmortem examination was made, it seems quite possible to exclude the factor of trauma at the time of the first operation. The entire cystic duct and a tiny stump of the gallbladder were still present, and it is difficult to see how such a process of sclerosis, which was generalized throughout the whole duct system, could be produced by a local injury to the duct. Microscopic examination of the duct likewise tends to further the view that the process was inflammatory in origin, as the microscopic studies revealed a chronic fibrous type of cholangeitis with evidence of moderately active infection still present (fig. 2).
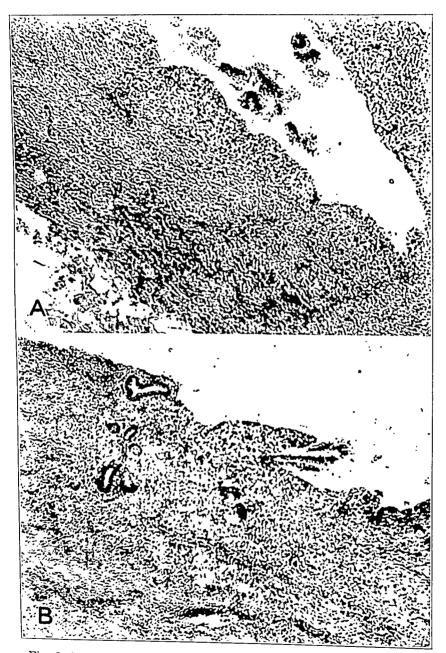
Fig. 2 (case 2).—*A*, obliterating cholangeitis involving the hepatic duct; *B*, similar involvement in the common duct. In this case the process still shows evidence of considerable activity; × 80.

Whipple [12] reported a second case which, because of its resemblance to this last one, should be mentioned here.

A man was found to be a typhoid carrier and for this reason was advised to have his gallbladder removed. At the time of operation the gallbladder as well as the common duct appeared to be the site of chronic inflammation. At the time of the removal of the gallbladder a large portion of the cystic duct was left intact. Convalescence was without event. However, seven or eight months later, jaundice developed and persisted for two or three months. A second operation was performed. At this time complete fibrosis of the common and the common hepatic ducts was found, but there was dilatation of the right hepatic duct, and an anastomosis was made between the right hepatic duct and the duodenum. The patient did well for four days, when a separation at the suture line occurred and peritonitis developed. Whipple stated that he was sure that in this case no trauma had been responsible, because the onset of the jaundice was so delayed. He felt that the condition was undoubtedly the result of a chronic inflammation of the entire efferent duct system.

COMMENT

From the histopathologic standpoint our two cases show essentially the same process in the extrahepatic bile ducts, that is, a chronic obliterating cholangeitis, the process in case 2 being somewhat more active than that in case 1. In both instances the clinical syndrome of obstruction of the common duct with jaundice was produced, and in each instance a clinical diagnosis of stone in the common duct was made.

In case 1 there can be no doubt that the process was inflammatory from the beginning, as the usual factors of operative trauma and irritation or ulceration from stones can be ruled out. In case 2 a cholecystectomy had been performed, and at that time, the gallbladder contained stones. However, the diffuse character of the lesion of the ducts, the absence of stones in the common duct at the time of the second operation and the failure to find any localized stricture would tend to bar from consideration these traumatic factors, while the microscopic studies tend to substantiate the view that we were dealing with a diffuse inflammatory process.

As Miller pointed out, in this group of cases there seems to be nothing characteristic in the clinical findings which might cause one to surmise the actual condition. A preoperative diagnosis in the reported cases was made of obstruction of the common duct probably due to gallstones or cancer, and the true nature of the condition was disclosed only at the time of operation. In fact, there seem to be no reliable criteria by which the diagnosis can be definitely made, although Miller believed that when there is considerable delay in the appearance of jaundice in the patient with a long history of recurrent attacks of biliary colic, one might suspect the condition. Also, the presence of progressive jaundice without remission, in the absence of demonstrable enlargement of the gallbladder, might point to an inflammatory closure of the duct.

Fig. 3.—Control sections of (A) normal hepatic duct and (B) normal common duct; × 80.

Regarding therapy, when the entire system of extrahepatic ducts has become involved, the problem of treatment is a difficult one. If technically feasible, and the gallbladder is found to contain bile, cholecystenterostomy seems to be a logical procedure and is probably worth while, although with extreme narrowing of the hepatic ducts it is easy to see how even this may be unsuccessful, while in the case of a small contracted gallbladder such an anastomosis may not be possible. If the hepatic duct remains uninvolved, the decision may be simpler, as in such a case hepaticoduodenostomy might be performed.

TUMORS OF THE SALIVARY GLANDS

J. D. MARTIN, M.D.

AND

DANIEL C. ELKIN, M.D.

ATLANTA, GA.

Tumors of the salivary glands constitute a large number of the lesions in the neck and on the face. The so-called mixed cell variety is the most frequent of these growths, although primary carcinomas occur. The close relationship of these lesions to the true malignant growths makes it impossible to separate them. Previous investigations have been directed largely toward a study of the pathogenesis, and but little emphasis has been given to the clinical course. Therefore, a review of the probable pathogenesis, the clinical course and the treatment is given, with a report of twenty-four cases.

According to the appearance of the tumors, various names have been given: fibromyxoma, myxoma, fibromyxo-endothelioma, endothelioma, chondroma, chondrocarcinoma, adenoid cystic epithelioma, cylindroma and many others. Needless to say, they are descriptive only of the type of tissue. The benefit derived from such terms is merely that of a catalog, although the primary purpose of a pathologic classification should be to show, so far as possible, the clinical course and prognosis in an individual case. It must be remembered that benign tumors of the salivary glands may become malignant, and that an incorrect prognosis may be made if they are seen before or during the period of metaplasia.

THEORIES OF FORMATION

Opinions regarding the pathogenesis of the mixed tumors of the salivary glands have been diverse, but, for the most part, these tumors may be considered to be (1) epithelial, (2) fibro-endothelial or (3) fibro-epithelial in origin. Since there is a participation in these tumors of both mesenchymal (connective tissue, mucus and cartilage) and ectodermal (gland, tubules and epithelium) embryonic tissues, such lesions are justly considered to be of the mixed variety. Kux[1] stated that the absence of certain epidermoid cellular content, such as fibrillation of the protoplasm, intercellular bridges and keratohyaline granules, does not speak against their epithelial nature, as epidermoid cellular contents

cannot be expected in juvenile, nondifferential epithelial cells or in cells that have been transformed into flat epithelium. Concentric formation in mixed tumors may be indicative of epithelial as well as endothelial origin. The demonstration of elastic fibers in the wall of concentric formations may speak in favor of endothelial genesis. If they are derived from endothelium, they originate from the vessels that have undergone hyaline degeneration. In the absence of elastic fibers there is no proof of nonendothelial origin, as they may be destroyed in the walls of the vessels, which have undergone changes.

All these mixed tumors of the salivary glands were originally considered to be carcinomas, especially by German writers. Virchow believed that the cartilage was derived from the metaplasia of connective tissue, although Cohnheim and others considered it to be a remnant of the branchial arches. The endothelial theory was first advanced in 1879 by Hartman, who stated that the polyhedral cells were derived from lymphatic endothelium. This theory was doubted by several investigators, particularly by Hinsberg, who expressed his views in 1899. The attempt was made to prove, by embryologic studies, that the tumors arose from invagination of buccal epithelium, with the inclusion of mesoblastic tissue connected with the mandible arches. These facts have made acceptable the dual origin of the tumors, namely, ectodermal and mesodermal, with wide variations due to the degrees of predominance of one of the groups.

The greatest evidence rests with the proponents of the epithelial origin. On the basis of extensive study, Krompecher concluded that these mixed tumors are epithelial in origin.[2] He found that the epithelial cells split off, fibrillate and take on the shape of mucoid or embryonal connective tissue. It has not been determined whether the epithelium is derived from the salivary glands. This theory is tenable for established growths, but some of the early growths exhibit no relationship to the ducts or acini. This apparent defect in an otherwise sound theory may be corrected by the utilization of the branchial origin without disturbing the regular laws of the histogenesis of tumors. Although the epithelial theory is generally accepted in this country, it is not universally approved.[3]

INCIDENCE

Mixed tumors of the salivary glands occur at all ages, although they are found most often in the fourth decade. Of the twenty-four cases reviewed, twelve occurred during this period, and six occurred during

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2. Greenberg, H.: Thirty Cases of Mixed Tumors of the Salivary Glands, Arch. Clin. Cancer Research **4**:141 (Jan.) 1929.

3. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1927.

the fifth decade. The youngest patient was 26 years old, and the oldest was 76. There was an equal number of males and females. The parotid was the gland most often affected. The submaxillary gland was involved in only three instances, and no tumor of the sublingual gland was encountered. The majority of the cases were in middle-aged patients, probably because at this period the tumor takes on activity after quiescence of from two to twenty years, and this rapid growth causes the patient to consult a physician. At this stage there is definite evidence of change from a benign growth to a rapidly growing malignant process.

PATHOLOGY

Pathologically, these tumors should be divided into two main groups: first, those seen early, in which there is a predominance of the mesoblastic tissue, and, second, those which are more cellular. In the former group the tumor has been present for a long period and is extremely firm; it is usually flattened and fixed to the substance of the gland itself, although it is sharply outlined and movable. Occasionally these tumors are irregular in shape, and they are often nodular, but most of them are characterized by regularity and apparent innocence, until some outside disturbance causes increased activity. A thick fibrous capsule surrounds the tumor, the weakest part of which is usually located nearest the normal glandular tissue. On section there are whitish-yellow strands of pale glistening, translucent mxyomatous tissue. Between these bundles a softer and more elastic tissue is seen. Differentiated cartilaginous tissue is rarely found on gross examination, but microscopically it is often seen. Histologically, in the first group there are cords of polyhedral dark hyperchromatic cells which occupy the region between the strands of thick hyalinized fibrous stroma. When the cartilage is present it appears as small sheets which occupy an acellular region. Occasionally there is an attempt to form palisades by piling up of the cells.

In the second pathologic class, the growth is also encapsulated, but is much softer than in the former group. The tumor either appears to be a part of the salivary gland or is separated from it by a fibrous capsule. These tumors are representative of the epithelial predominance which is noted after opening the capsule in that there is a diminution of fibroblastic stroma. The substance of the mass is extremely friable and sometimes necrotic. Microscopic examination shows large groups of dark hyperchromatic cells, which are more uniform in size and shape than in the first group. The number of mitoses present depends on the activity of the tumor. In sections small strands of densely organized fibrous tissue are seen surrounding the cells. There may be attempts at gland formation. Occasionally the acini are perfectly shaped and surrounded by thick plaques of fibrous or chondral tissue. However,

the acini that do occur are immaturely formed and are usually located nearest the normal glandular tissue.

CLINICAL COURSE

The course of mixed cell tumors of the salivary glands is usually characteristic. As a rule, the history is that the tumor was noticed first as a small pea-shaped swelling in the region of the gland, which was given no consideration, because there was no pain or variation in size. The onset is frequently thought to occur following septic parotitis or trauma, although this relationship is probably coincidental. After many years of remaining dormant, there is increased activity, which varies with the type of cell and in which trauma may be an exciting factor. If the tumor is removed at this time, it is usually found to be benign, both grossly and histologically. When removal has been incomplete, as is frequently the case, there is usually a recurrence within from a few months to two years. Growth is more rapid than that of the original tumor. The adjacent cervical lymph nodes are not involved unless the tumor is primarily malignant.

There are few conditions from which these tumors must be differentiated. Various lymphoblastomas that involve the nodes nearest the salivary glands probably offer the most trouble. Frequently a definite diagnosis is not made until the tissue has been examined microscopically. A large calculus in the duct of the parotid, with a chronically inflamed gland, caused confusion in one instance. The diagnosis was evident when a roentgenogram was taken, which should always be done if there is an unusual history, particularly in the presence of marked pain. Pain is absent except in cases in which the sensory nerves are involved. Sebaceous cysts must be considered, especially when the lesions are smooth and ovoid and have been present for a long period. Growths which have undergone cystic changes cause the greatest difficulty, whereas typical tumors are less confusing. Removal is often required before a diagnosis is made, although it is best to consider all such growths of glandular origin until they have been proved otherwise.

TREATMENT

During recent years there has been a widespread use of radium and roentgen rays, but the results in our cases do not support their use alone.[4] The opinion of the physicians at the Steiner Clinic is similar to that of Sistrunk,[5] who believed that surgical removal gives the best results.

4. Merritt, E. A.: Mixed Tumors of the Parotid Glands, Am. J. Roentgenol. **25**:507 (April) 1931.

5. Sistrunk, quoted by Patey, D. H.: The Mixed Tumors of the Salivary Glands, Brit. J. Surg. **18**:241 (Oct.) 1930.

Certain tumors show radiosensitivity, and it is these which have a predominance of cellular elements. As a rule, complete regression of the tumor following irradiation is unusual. It is probably beneficial to precede operative removal with a complete course of high voltage roentgen therapy, both for its therapeutic effect and for its value as an indicator of cellular activity.

Thus, the main therapeutic measure must be complete extirpation of the tumor. In an effort to prevent injury to the facial nerve and the soft structures there is always the danger of failure to remove all the diseased tissue. Although it is well in some instances to attempt to preserve the nerve, it must be remembered that only by total removal of the tumor can a permanent cure be effected. Since the facial nerve passes through the parotid gland, it is evident that it would be injured in complete excision of the gland. If the main branch of the facial nerve is severed at the time of the operation, there is a possibility of anastomosing the cut end of the nerve to the spinal accessory or hypoglossal nerve and, by reeducation of the patient, establishing a sufficient nerve supply to the muscles of the face. The inconvenience of peripheral facial nerve paralysis is offset by the knowledge that the tumor has been completely removed.

In several of our cases implantations of radium seeds were made at the time of the operation and high voltage roentgen therapy was used later. This was done in cases in which there had been a previous recurrence and in which it was thought to be impossible to remove the remaining tissue completely without damage to the deep structures. The results of such a procedure have been encouraging, particularly when the tumors were definitely malignant.

COMMENT

The inconspicuous onset and apparent innocence of the growth cause the patient to delay in seeking treatment. The earliest tumor seen in this series had been present only seven months. Twenty years was the longest period before treatment, the average period being between seven and twelve years. It is readily seen that if treatment is given early there is a greater opportunity of completely effecting a cure before the tumor becomes malignant.

Twenty-one cases were of the mixed cell variety, of which eleven were definitely benign. The remaining ten showed evidence of low grade carcinomatous changes. Three cases in the series showed adenocarcinoma of the salivary gland, which is not a high incidence of primary malignancy in this organ. Whereas, in several instances malignant changes were present along with those of the mixed type, it is well to assume that the original lesion was benign. This fact was verified by the clinical course of the tumors.

A combination of surgical removal with the use of roentgen therapy and radium prevented recurrences in only seven cases. There was recurrence of the growth in ten cases. Twelve patients are still living, although there have been recurrences in several. In seven instances the result is unknown. Five patients are known to have died within from a few months to three years after being treated. From these facts it is evident that the prognosis is not good, as the possibility of reappearance of the lesion is very great, recurrence having taken place in more than two thirds of the cases studied. The primary growth should first be completely removed; by this means only can recurrences be prevented. However, when there is a recurrence, it must be treated more actively than the original tumor, because with each recurrence there is a tendency for the growth to become more active, thereby making permanent cure less likely.

REPORT OF CASES

CASE 1.—Mrs. R. E. B., aged 28, was admitted to the Steiner Clinic on Sept. 29, 1930, with a small nodule at the angle of the jaw on the right side, which was first noticed eight years before. The swelling had been gradual, and the growth measured 5 by 5 by 4 cm. The mass was firm and only slightly movable. On October 25, an encapsulated tumor was removed.

Pathologic examination showed that one portion was firm, white and nodular. The remainder was soft and vascular. There was no gritting on cutting. Sections showed an edematous, mucoid structure, with large vacuolated areas surrounded by small hyperchromatic cells. No true glands were seen. These areas were surrounded by dense connective tissue. In other portions large hyaline bundles were found, with small hyperchromatic cells alongside. No cartilage or bone formation was seen.

The diagnosis was mixed tumor.

CASE 2.—Mrs. R. D. C., aged 44, was admitted on Oct. 4, 1929, to the Steiner Clinic, with a tumor mass in the region of the left parotid, which had been present since 1922. Growth had been gradual but steady until 1924, when both roentgen rays and radium were used elsewhere. A period of quiescence followed this treatment, but there was no diminution in the size of the tumor. A symmetrical cone-shaped tumor mass was seen extending in front, below and behind the lobe of the left ear; it measured 4.5 by 4 cm. The skin over the mass showed marked effects of irradiation, with scattered areas of telangiectasia. On October 8 the tumor was removed. In the center gold tubes of radium were found, which had been inserted elsewhere.

Pathologic examination showed an extremely friable and edematous tissue mass, measuring 5 cm. in diameter. There was a very cellular structure composed of medium-sized and small polyhedral cells lying in an edematous fibrous hyaline or myxomatous matrix. The cells showed a clear cytoplasm and degenerated hyperchromatic nuclei. There was no cartilage formation.

The diagnosis was mixed tumor.

On Aug. 15, 1930, about ten months after the operation, there was a firm area 2 by 1 by 1 cm. in front of the scar just under the ear. On Sept. 18, 1931, the patient was operated on again; gold tubes of radium were inserted, and 1,808 millicurie hours of exposure were given. Following the treatment there was a

marked reaction to irradiation and an ulceration developed which required one year for healing. There was no evidence of disease on Jan. 18, 1933.

CASE 3.—Miss L. H., aged 55, was admitted to the Steiner Clinic on July 5, 1929. Two years before, a small lump was noticed in front of the left ear at the angle of the jaw. Growth was progressive until April, 1929, when the mass was opened by her physician, and a small quantity of bloody material was removed. On admission the mass was elongated and firm but not hard, and measured about 2 by 0.5 cm. It was located just below the lobe of the left ear. The tumor was removed with much difficulty on July 13. A portion of the facial nerve was severed.

The tumor mass measured 2 cm. in diameter and was soft and translucent. Sections showed large areas of myxomatous structure together with small areas of beginning cartilage formation. Scattered throughout were clumps of small hyperchromatic epithelial cells without gland formation. One point showed a small area of parotid acini.

The diagnosis was mixed tumor, with a tendency toward malignancy.

CASE 4.—Mrs. C. E. R., aged 56, was admitted to the Steiner Clinic on June 29, 1932, with a small, freely movable tumor mass behind the right ramus of the mandible beneath the ear and attached to the underlying structures. This mass was noticed in 1928, at which time the patient had Vincent's angina. On July 5 the tumor was removed.

Pathologic examination revealed an encapsulated tumor mass 4 cm. in diameter, rounded, slightly lobulated and cystic. The color was reddish blue. A cross-section showed cystic areas with a mucoid secretion. There was an acellular stroma, rather loose and edematous, in which were small collections of hyperchromatic epithelium. No diffuse cellular areas were seen. Large areas were composed of myxomatous structure. In a few areas definite gland formation was present.

The diagnosis was mixed tumor of low grade malignancy.

CASE 5.—A. C., aged 75, was admitted to the Steiner Clinic on June 14, 1929, with a small tumor at the ramus of the left mandible which had been present for twenty years. There had been no appreciable variation in size. The mass was freely movable and firm and measured 4 by 4 by 3 cm. On June 21 the tumor was removed.

Pathologic examination showed a multiloculated cystic mass 3 cm. in diameter with some mucoid areas. There were masses of hyaline connective tissue with scattered areas of sheets and strands of hyperchromatic polyhedral epithelial cells, and some edematous and myxomatous areas, but no cartilage or gland formation.

The diagnosis was mixed tumor.

CASE 6.—W. H., aged 47, was admitted to the Steiner Clinic on Feb. 2, 1931, with a hard mass about 3 cm. in diameter in front of the right ear. There were also several firm nodes in the submaxillary triangle of the neck. The entire tumor mass was removed and a dissection of the glands of the neck was done on February 11. Nineteen gold tubes of radium of 12 millicuries were implanted at the time of operation.

Pathologic examination showed abundant mucoid material but no calcification or cartilage. Sections showed broad sheets of medium-sized and small cells, acidophilic in reaction. There were an abundant hyaline stroma in broad bands and an excessive amount of basophilic mucoid material. Mitoses were scanty.

The diagnosis was mixed tumor.

On April 24 there was no evidence of disease.

CASE 7.—H. H. P., aged 42, was admitted to the Steiner Clinic on May 17, 1929. He stated that twenty-two years before a small tumor was noticed in front of the right ear, which grew very slowly for eight years to about 1 cm. in diameter. In 1917 the mass was removed, only to recur soon afterward. Just behind a curved ¾ inch (1.9 cm.) scar in front of the right ear were four flattened, firm, smooth tumors, which were freely movable and not tender. On May 20 the nodular tissue with mucoid material was removed.

Sections showed a varied structure containing islands of small polyhedral hyperchromatic epithelial cells in irregular arrangement, lying in a hyaline matrix of basophilic mucoid stroma. Other portions showed epithelium lining small glandular cavities.

The diagnosis was mixed tumor of the parotid.

On May 27 and 30 and June 4 a course of roentgen therapy was given.

CASE 8.—H. E. P., aged 32, was admitted to the Steiner Clinic on Feb. 16, 1929, with a tumor in the left side of the face, which had been present for twelve years. This had grown very slowly until five years before examination, at which time the patient was given roentgen therapy. The swelling was reduced materially for about one year, and then the tumor began to grow more rapidly. It was removed by the patient's physician on Jan. 20, 1929.

Pathologic examination showed a large number of strands of small epithelial cells, which were slightly hyperchromatic. The bulk of the tumor was made up of hyaline acellular tissue appearing in bundles supporting the epithelial cells. There was no evidence of gland formation, cartilage or myxomatous structures.

The diagnosis was tumor of the parotid, basal cell carcinoma with hyaline stroma.

The tumor promptly recurred and was again removed; sections showed mixed tumor approaching malignancy. There was a second recurrence, after which the tumor was removed on about Dec. 6, 1932, by the patient's physician. At this time the sections showed masses of scar tissue, with hyperchromatic polyhedral epithelial cells arranged in rounded masses. The central portion was loose and was filled with a basophilic faintly granular material. There was considerable hyaline stroma. The patient has had four courses of roentgen therapy.

CASE 9.—Mrs. L. W. E., aged 47, was admitted to the Steiner Clinic on Sept. 9, 1931, with a swelling in front of the left ear. About six years before the patient had had the mumps, and the left side of the face had been enlarged since. Growth was rapid for four months. About two weeks before her admission to the clinic she went to her physician, who opened the swelling and removed a portion of the tumor. After the operation the swelling increased in size, and a small fistula remained. The mass measured 3 by 4 by 2 cm. It was hard and slightly movable. The patient was advised to have the entire tumor removed, but refused. A biopsy was done, and eight gold tubes of radium were inserted (2,021 millicurie hours). One treatment with roentgen rays was given.

Pathologic examination showed large areas of hyaline cartilage with many epithelial cells. There was no gland formation.

The diagnosis was mixed tumor.

CASE 10.—W. C., aged 38, was admitted to the Steiner Clinic on May 3, 1932, with an enormous mass at the right side of the lower jaw. The swelling had begun twenty years before as a small nodule about the size of a pea at the angle of the jaw. Growth was slow but gradual until just before the patient's admission to the Clinic, when it became more rapid. About March 1, 1932, a small nodule was noticed in the left side of the neck. The mass was elongated, very hard and lobu-

lated and extended from the angle of the jaw downward to the clavicle and in front to the midline. On May 6 the entire mass, which weighed 850 Gm., was removed.

The cut surface showed large areas of necrosis, considerable bone and cartilage. Sections showed large sheets of hyaline cartilage with small areas of myxomatous structure and masses of small acidophilic cells of the salivary gland type. There were also sheets of large hyperchromatic cells, many of which were pavement cells. Mitoses were moderate in number. Scattered areas of necrosis were present.

The diagnosis was mixed tumor of salivary gland origin, radioresistant carcinoma.

On July 24 there was a return of the tumor, and the patient went to another hospital for roentgen therapy. Following this treatment there was no regression, and the patient died six months after the removal of the tumor.

CASE 11.—Mrs. G. D., aged 29, was admitted to the Steiner Clinic on June 30, 1930, with a swelling in the upper part of the left side of the neck. Eleven years before admission, following typhoid fever, the patient had noticed a small node under the angle of the jaw on the left side. The mass gradually enlarged to about 3 cm. in diameter. It was hard, but freely movable. On June 30 the tumor was excised.

Pathologic examination showed an encapsulated tumor 3.5 cm. long and 2 cm. wide. The cut surface was white and firm, with scattered translucent areas. Sections showed poorly formed acini lined with small acidophilic and moderately hyperchromatic epithelial cells. In other areas these cells were in diffuse sheets with myxomatous structure. There were many areas of hyaline cartilage with early calcification.

The diagnosis was mixed tumor, myxochondrocarcinoma.

On Nov. 22, 1932, there was no evidence of disease.

CASE 12.—Mrs. A. V. S., aged 50, was admitted to the Steiner Clinic on Jan. 9, 1930, with a tumor near the angle of the jaw on the right side. Eleven years before a tumor in front of the right ear had been removed; it had been present for many years. The type of this tumor was never ascertained. There was a slow recurrence of the growth in the region of the operative scar. There had been much loss of weight during the previous months. A hard indurated flat mass extended from the angle of the jaw forward to the center of the mandible and upward to just below the zygoma and behind the ear. There was a bluish discoloration on the surface of the skin in the region of the old operative scar. In view of the wide extent of the tumor, operative removal was not attempted, but the growth was treated for two and a half years with roentgen rays at regular intervals, with marked changes. No biopsy specimen was obtained. On Dec. 9, 1932, there was no evidence of disease.

CASE 13.—Mrs. N. G., aged 60, was admitted to the Steiner Clinic on Aug. 4, 1932, with a mass in the left side of the neck just under the chin, which had been present for a year. Growth had been very slow. The tumor was slightly tender and measured 4 cm. in diameter. On August 25 the mass was removed, and radium implants were placed in the neck.

Pathologic sections showed abundant acellular connective tissue with considerable calcification. There were a few scattered areas of medium-sized and small moderately hyperchromatic epithelial cells, with an occasional mitosis. One area showed mucoid degeneration.

The diagnosis was mixed tumor of salivary gland origin, radioresistant carcinoma of low grade malignancy.

The patient was readmitted to the Clinic on October 10 and died on October 13. Autopsy revealed metastatic carcinoma of the liver and chronic nephritis.

CASE 14.—Mr. E. H., aged 56, was admitted to the Steiner Clinic on Aug. 4, 1932, with a swelling of the left side of the face. About a year before he had had a tooth pulled, and immediately after this a lump was noted in the left side of the face. This grew very slowly and became somewhat painful. Various ointments and poultices were applied until the swelling became ulcerated. There was a hard mass beneath the left ear, extending down in the neck for about 1 inch (2.5 cm.). An ulceration was in the center of the mass about ½ inch (1.2 cm.) in diameter. There was facial paralysis.

Biopsy showed extensive necrosis, with abundant dense connective tissue in which were many strands of medium-sized hyperchromatic epithelial cells without acini formation. There was an occasional mitotic figure.

The diagnosis was radioresistant carcinoma simplex.

CASE 15.—J. E. McI., aged 47, was admitted to the Steiner Clinic on April 2, 1929, with a swelling on the right side of the face. This was first noticed seventeen years before when he had received a blow on the face. It remained stationary until eighteen months previous to admission when it began to grow and cause pain on eating. Just in front of the right ear was a hard tumor 3.5 cm. in diameter. It was fixed on movement of the jaw. On April 5 a partially encapsulated tumor was removed. There was an abundant fibrous stroma in which were large islands of medium-sized hyperchromatic cells showing occasional mitoses. The connective tissue was acellular. Section of two lymph nodes showed them to be the seat of metastases.

The diagnosis was carcinoma of the parotid, with metastases to lymph nodes.

CASE 16.—J. R. R., aged 43, was admitted to the Steiner Clinic on March 12, 1928, with pain in the left side of the jaw. Four years before he had been operated on for a thickening in front of the ear. No definite tumor was found, and no tissue was removed. There had been marked pain and fulness in the region of the left ear. At the angle of the jaw, just in front of the mastoid process, a tumor was felt, which was firm and apparently arose deep within the neck and extended well forward. On March 30 the tumor was exposed, but could not be removed, owing to the depth and extension. A biopsy specimen was taken, which showed masses of connective tissue in which large alveoli were filled with small hyperchromatic cells arranged around a large lumen filled with mucoid material.

The diagnosis was adenoma-carcinoma of salivary gland origin.

The patient received several courses of roentgen therapy, with no benefit. Death occurred in 1931. Autopsy showed metastases to the pleura.

CASE 17.—G. B., aged 23, was admitted to the Steiner Clinic on May 27, 1925, with a lump in the left side of the face. The tumor had been present for twelve years. It grew very slowly for two years, after which it was removed by the patient's physician. A few months later it was noticed that the tumor was recurring. At the lower pole of the left parotid a smooth, firm, globular, movable tumor was found, which measured 3 cm. in diameter. The skin was adherent to the tumor. Two small nodules were felt below this main mass. Preoperative irradiation was given, and on June 12 the tumor was removed.

Pathologic examination showed dense tissue, which cut with some difficulty and showed mucoid material with large areas of hyaline cartilage and small areas of glandular structure.

The diagnosis was mixed tumor of the parotid.

There was no evidence of the disease when the patient was last seen.

CASE 18.—R. B. R., aged 44, was admitted to the Steiner Clinic on June 6, 1925, with a tumor in the left side of the face, which had been present for ten years. Two years before admission the tumor began to enlarge and cause considerable pain. Roentgen therapy was given, with some retardation of the growth. Immediately below the left ear between the angle of the jaw and the mastoid process was a hard, smooth, fixed, flat tumor mass measuring 4 by 3 cm. In the posterior triangle of the neck were firm fixed lymph nodes, from 0.5 to 2 cm. in diameter. Two radium treatments in the form of a pack were applied to the upper and lower tumors. On June 20 a node was removed; this showed dense masses of connective tissue with many tumor cells. The cells were large, with hyperchromatic nuclei, and were fused. There were other areas of polyhedral cells with hyperchromatic nuclei.

The diagnosis was carcinoma of the parotid.

The patient died on December 6.

CASE 19.—Mrs. F. M. L., aged 54, was admitted to the Steiner Clinic on Aug. 6, 1926, with a large tumor in the region of the left parotid gland. On July 21
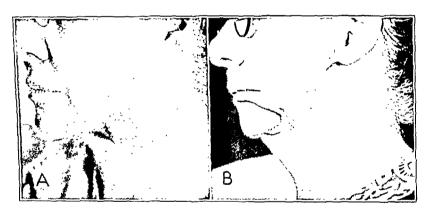
Fig. 1 (case 19).—*A*, photograph of patient taken in 1926, showing primary tumor of the parotid; *B*, photograph of patient taken in 1930, after secondary operation of resection of the mandible followed by a bone graft.

an encapsulated tumor was removed, which measured 9 by 6 by 4 cm. Sections showed diffuse sheets of rounded cells with a fairly clear cytoplasm and a well marked nucleus and nucleolus. There was much hyaline material, into which the cells gradually merged. Other areas showed diffuse growths of epithelium of small rounded and polyhedral cells with hyperchromatic nuclei, forming atypical glands and ducts.

The diagnosis was mixed tumor of the parotid, adenocarcinoma.

On July 8, 1929, recurrence was noted, and a biopsy section was taken to confirm this fact. Gold tubes of radium were placed in the tumor. On Dec. 16, 1929, roentgen therapy was begun. On Jan. 10, 1930, roentgenograms showed destruction of the left side of the mandible. Resection of the left side of the mandible was done, which showed metastases to the mandible. Dissection of the neck was done on Feb. 14, 1931, after there was a recurrence of growth in the anterior chain of the cervical lymph nodes. On November 20 a bone graft was placed in the defect in the mandible. On March 28, 1932, metastases were noted in the left occipitoparietal region of the skull. Four months later there was no

increase in the size of the metastases. The patient had six complete courses of roentgen therapy, including treatment of the process in the supraclavicular nodes and the skull, from 1926 to the time of admission. Gold tubes of radium were inserted in the nodes and recurrent growths on three occasions. On Jan. 9, 1933, the patient was living and doing nicely; there was no further evidence of recurrences.
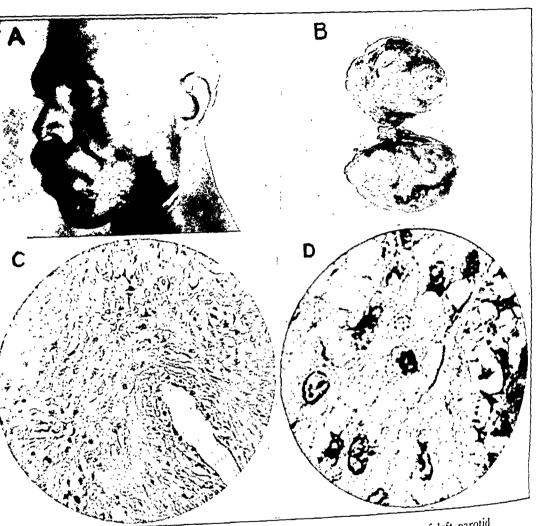
Fig. 2 (case 20).—*A*, photograph of patient, showing carcinoma of left parotid gland; *B*, gross appearance of tumor removed at first operation; *C*, low power magnification, showing cellular character of the growth; *D*, high power magnification, demonstrating mitosis.

CASE 20.—T. C. E., aged 49, was admitted to the Grady Memorial Hospital on Aug. 3, 1932, with a tumor in the left side of the face, which had been present for twenty years. It had been about 1 cm. in diameter until about eight months before admission, when it began to grow and cause some pain. An ovoid tumor mass measuring 3 cm. in diameter was felt at the angle of the jaw. It was firm

and fixed to the surrounding structures. The tumor was removed, along with a portion of normal parotid tissue, without injury to the facial nerve.

Sections of the tumor showed numerous epithelial cells, which were surrounded by dense strands of connective tissue. There were numerous mitoses in the epithelial cells, and many polymorphonuclear leukocytes were present.

The diagnosis was carcinoma simplex.
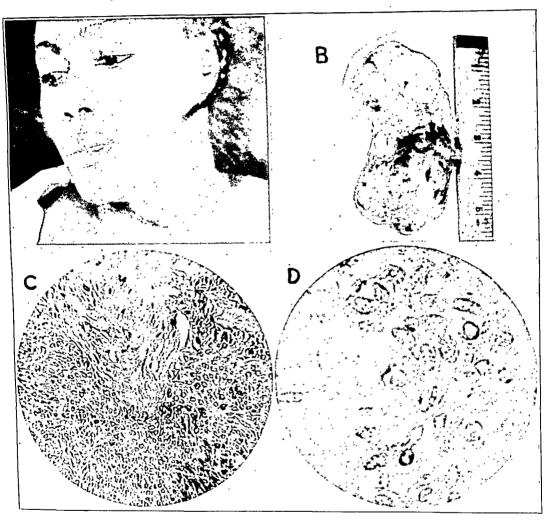
Fig. 3 (case 21).—*A*, photograph of patient, showing mixed tumor of the left submaxillary gland; *B*, gross appearance of cross-section of tumor; *C*, low power magnification, demonstrating the two types of tissue; *D*, magnification showing character of cells.

On Jan. 28, 1933, there was a recurrence of the tumor to twice the size before the first removal. A complete course of roentgen therapy was given, without regression. The entire parotid was removed on March 10, and radium was implanted in the wound (2,000 millicurie hours).

Sections of the recurrent tumor showed a very active carcinoma of the parotid gland.

CASE 21.—M. J. was admitted to the Grady Memorial Hospital on Feb. 27, 1932, with a tumor in the left side of the neck. The swelling was noticed seven years before admission after an attack of sore throat. Growth had been slow but progressive. The tumor was felt under the lower border of the mandible; it was freely movable but firm. On February 28 the mass was removed and was found to be encapsulated. It measured 6 by 5 by 4 cm.

On cut section the tumor was firm and had a hard gritty feeling. Microscopic examination showed immature alveoli. There were many hyperchromatic cells, which were regular in size. There were large bands of acellular fibrous stroma, with scattered areas of cartilage.

The diagnosis was mixed tumor of the salivary gland.
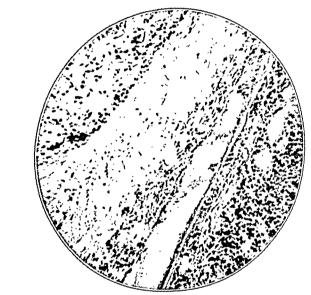
Fig. 4 (case 23).—Appearance of typical tumor under low power magnification.

CASE 22.—L. K., aged 56, was admitted to the Grady Memorial Hospital on Oct. 10, 1931, with a tumor mass in front of the left ear, which had been present since February. Growth had been rapid during recent months. Examination showed a firm tumor about 2 cm. in diameter just in front of the left ear. The tissue was grayish yellow and quite firm. Sections showed an extremely cellular tissue, with a small amount of stroma. The cells contained many mitotic figures. There were areas that contained a compact hyalinized cellular tissue.

The diagnosis was carcinoma of the parotid.

The tumor recurred within a few months and was treated with radium at the Steiner Clinic.

CASE 23.—C. W., aged 44, was admitted to the Grady Memorial Hospital with a tumor in the region of the right parotid. The swelling had first been noticed two years before and had grown gradually since. The mass was firm and ovoid in shape, occupying the region of the right parotid gland. It was well encapsulated and measured 6 cm. in diameter. There was much firm, cartilaginous tissue scat-

tered throughout. Many hyperchromatic cells were located between the strands of fibrous connective tissue.

CASE 24.—M. F., aged 45, was admitted to the Grady Memorial Hospital in September, 1932, with a tumor mass in the left submaxillary region, which had been present for two years. The tumor was well encapsulated, freely movable and not tender. It measured 6 by 5 by 4 cm. On section the center was found to be extremely necrotic and friable.

Pathologic examination showed many large hyperchromatic cells surrounded by strands of dense fibrous connective tissues. Mitoses were present.

The diagnosis was mixed tumor with early malignancy.

SUMMARY

1. The so-called mixed tumors constitute the largest number of growths of the salivary glands.

2. The most widely accepted theory of the formation of mixed cell tumors of the salivary glands is that of an epithelial origin, although there is still some difference of opinion concerning their exact nature and formation.

3. Pathologically, these tumors may be grossly divided into two classes, depending on the predominance of the embryonal tissue. The more cellular the tumor, the more likely is recurrence when the growth has not been completely removed.

4. The use of roentgen rays and radium and early removal of the primary growth offer the greatest hope for cure.

5. The prognosis, based on a study of the treatment in twenty-four cases of tumor of salivary gland origin, is not good either for complete cure or for prevention of recurrence.

6. Following the removal of the original tumor, the recurrent growth becomes more malignant.

EXPERIMENTAL BONE TRANSPLANTATION
WITH SPECIAL REFERENCE TO THE EFFECT OF "DECALCIFICATION"

RALPH K. GHORMLEY, M.D.

AND

WALTER G. STUCK, M.D.

Fellow in Orthopedic Surgery, the Mayo Foundation

ROCHESTER, MINN.

In recent years, many of the old, well established concepts of the physiology of bone have been profoundly altered in order to become adapted to the newer beliefs. No longer is each histologic division of adult bone singled out by some one group of investigators as the sole bone-forming element. The belief is growing that the processes of osteogenesis, regeneration of bone and healing of bony defects are far more complicated than was previously thought. It is being recognized that these biologic manifestations are dependent on intricate biochemical or "humoral" phenomena with which investigators are but slightly familiar. As Leriche and Policard (1928) pointed out: "The problem of osteogenesis has passed through many phases. It has been histological and surgical and at the present time it is above all chemical. . . . It is now the turn of the chemists and physicists. They alone can open up new horizons by giving us some of the certainties which we lack."

CURRENT VIEWS ON FORMATION, CALCIFICATION AND DECALCIFICATION OF BONE

The authors just quoted, who are among the most thorough of modern workers, have elaborated the theory that all formation of bone is the result of metaplastic change in the connective tissue where bone is to be laid down. This metaplasia, they stated, takes place in three stages: (1) transformation of connective tissue by edematous infiltration, with multiplication of connective tissue fibrils; (2) infiltration by a special substance, clinically undefined, the preosseous substance; (3) deposits in that substance of a mixture of calcium phosphate and calcium carbonate, producing bone. Moreover, all formation of new bone at the sites of healing is accompanied by resorption of preexisting bone, and in fact depends on it, for as a result of the

rarefaction of bone, there is produced a localized oversupply of calcium which stimulates osseous metaplasia. This resorption of bone is accomplished by alterations in the local circulatory activity, which these investigators think is regulated by some humoral phenomenon.

Since 1923, Robison and his co-workers at the Lister Institute in London have amassed a wealth of evidence to strengthen the assumption that at least in the ossification of cartilage of young animals an enzyme ("bone phosphatase") is essential. The substance has been found to be very active in hydrolyzing the phosphoric esters of the blood corpuscles and plasma to release free phosphoric acid at the site of formation of bone. Thus, calcification is aided by enzymatic activity, and "the production of the enzyme is a part of the cellular activities which result in the formation of bone."

Keith proposed that there is an intimate relationship between vascular tissue and production of bone. He expressed the belief that formation of bone is engendered by the presence of a substance, or tissue, which stimulates the neighboring capillary system to throw out processes to bring about absorption in the body. In the invading vascular buds are cells (derived from the capillaries or from reticulo-endothelium) which may become osteoblastic or osteoclastic in their action. Keith stated also that he considers it essential that there be present a supply of suitable calcium salts in solution, and possibly some enzyme.

In each of these modern theories of growth of bone emphasis is placed on two basic beliefs: (1) that the calcium of the skeletal system is not a fixed, stable framework as much as it is a very accessible source of calcium to the blood stream, and (2) that all the phenomena of regeneration of bone are intimately dependent on vascular changes.

Relation Between Circulation and Calcification.—As early as 1908, Patterson pointed out that apart from their function as a supportive skeleton the bones were without doubt reservoirs of calcium. He expressed the belief that they acted as storers of calcium and that calcium could be lost, relative to the other salts, by selective autolysis. In 1929, Bauer, Aub and Albright reported that the trabeculae of cancellous bone served as a readily available supply of calcium and also that the trabeculae were more rapidly affected at the more vascular extremities of the long bones. In other words, the physiologic and even the morphologic characteristics of bone have been found to be closely bound up with the variations in its blood supply and with the fluctuating demands of the organism for "labile" calcium.

There is, furthermore, considerable clinical and experimental evidence to support the belief that atrophy or decalcification of bone is accompanied by an increased blood supply. And it is believed that alterations of the content of calcium (and of the vascularity) of the

skeleton produce definite changes in the rate of healing of bone. In our present work, we shall consider the effects of decalcification of animals, with the resultant increased vascularity of bone, on the healing of experimental bone transplants.

Decalcification and Atrophy.—Nearly sixty years ago, Förster first made the observation that with insufficient calcium in the food the muscles lost 60 per cent of their content of calcium and there was also considerable diminution in the calcium content of the bones. Shortly afterward, Voit discovered that the bones of an animal on a calcium-poor diet were more brittle than those of a normal animal, that the skeleton had a smaller dry weight and that the quantity of calcium in all the organs of the body was more or less diminished. Leriche and Policard recently stated that "in compact bone, enlargement of the haversian canals is the dominant sign of bone absorption" and that "this is always accompanied by circulatory increase." In such a process, the cellular structure is preserved and "the calcium phosphocarbonate disappears, like the glycogen of the hepatic cell or the fat of the adipose cell."

Jaffe has emphasized that resorption of bone is much more of a vascular and chemical phenomenon than an osteoclastic one. He stated that when there is a negative calcium balance the bone in the vicinity of the vascular canals becomes decalcified and the vascularity is increased. On the other hand, Radasch demonstrated that the atrophy of senile bone is primarily an osteoclastic phenomenon involving erosion of the cortex from the medullary cavity. This type of decalcification is distinct from and dissimilar to the vascular erosion which we are discussing.

With these considerations in mind, we became interested in the interrelations of atrophy, decalcification and the healing of bone. We attempted to determine whether when animals were decalcified by being given food low in calcium, distilled water and ammonium chloride the increased vascularity of the bones would lead to more rapid healing of bone. In other words, we wondered whether the healing of bone could be hastened if the bone were made more vascular and osteoporotic. Such a change is obviously a chemical one, widespread enough to cause a definite change in the process of ossification and formation of new bone.

This idea came about through the association, several years ago, of one of us (Ghormley) with Aub and Bauer, in the Massachusetts General Hospital. These workers were making some studies on the calcium balance, and Ghormley had a patient with scoliosis whom he wished to prepare for surgical intervention by stretching in a recumbent position over a period of several weeks. Aub and Bauer agreed to keep the patient in one of the beds of their service while the process of

stretching went on. At the same time, for their own study they kept the patient on a diet that produced a negative calcium balance. At the time of operation a decided decrease in the density of the bone was noted. The bone could be chiseled easily without the use of a mallet. After operation, when the patient was restored to a normal diet, rapid fusion at the site of operation on the spine took place. So rapid and satisfactory was the fusion that we have always thought that the "decalcification" previous to the operation had something to do with the result obtained.

<div align="center">REVIEW OF THE LITERATURE</div>

The literature on growth, regeneration and repair of bone has been surveyed often, and although these controversial matters have been frequently studied, we feel that it is a distinct contribution to assemble in outline all the available bibliographic material related to these subjects. In presenting this extensive summary of the literature, we make no claims to originality for the classification, because we have followed in part the outline utilized by Bull.

The theories of growth and regeneration of bone can be classified in five groups, each view being exemplified by the statement of an outstanding exponent: 1. Ollier (1867) maintained that growth and replacement of bone are due to specific osteogenic activity of the osteoblasts of the periosteum. 2. Barth (1893) said that all transplanted bone dies and is replaced by proliferation of new bone from the surrounding host bone into the dead transplant. The graft is osteoconductive. 3. Axhausen (1908) supported the view that repair of bony defects and the replacement of bone grafts are effected by deposition of bone by the periosteum and the endosteum. 4. Macewen (1912) claimed that bone grows and repairs itself by proliferation of the bone cells. The periosteum serves no osteogenic function and acts merely as a limiting membrane to the growing bone. 5. Baschkirzew and Petrow (1912) wrote that all new bone is formed by metaplasia of the preexisting connective tissue in the region where it is to be laid down.

Each experimental or clinical observation on some phase of physiology of bone we have abstracted and arbitrarily forced under one of these five theories. The obvious paradoxes and contradictions we shall pass without comment, for Groves and others have rationalized the divergent points of view most satisfactorily.

1. *Growth and replacement of bone are brought about by specific osteogenic activity of the periosteum.* Dellamotte (1694) in a case of compound fracture resected subperiosteally 6 inches (15.2 cm.) of a tibial shaft. Eight months later a new shaft had formed.

Duhamel (1742), in studying experimental fractures in animals which had been fed madder, determined that bone was laid down by the deep layers of the peri-

osteum (comparable to the cambium layer of growing wood) and that madder was deposited only in newly formed bone. He found that growth in the length of bones took place at the ends, but he did not study the epiphyses. Periosteum produced bone "as an exogenous stem grows from the inner layer of the bark."

Subperiosteal resection of bones of animals and man convinced Syme (1831) that bony defects were repaired by new bone laid down by the periosteum.

Flourens (1842) performed many experiments which corroborated Duhamel's view that new bone is deposited by the under layers of the periosteum.

Ollier (1867), in experiments on young dogs and other animals, found that transplanted periosteum produces bone, that suppuration does not prevent osteogenesis, that transplanted marrow does not produce new bone, that periosteal flaps or periosteal transplants are fully osteogenic in young animals but not in adults and that the power of osteogenesis, if lost to the adult periosteum, can be revived by stimulation of the compact bone beneath. He noted that if bone is resected without destroying the periosteum new bone forms and that transplanted bone dies when the periosteum alone is grafted.

Cushing (1899), following Nichols' idea, resected subperiosteally a necrotic tibia, closed the periosteum and found later that an entire new shaft was formed by the periosteum.

Grohé and Morpurgo (1899) found that after several hours' preservation outside the body, transplanted periosteum retained its vitality and osteogenic power.

Colvin (1907) performed subperiosteal resection of entire bones for osteomyelitis in several cases and later found that complete regeneration of their shafts had taken place.

Tomita (1908) stated that new growth is from the inner layer of the periosteum and from the marrow cells. The cells of the bone itself have no power to form new bone.

Nakahara and Dilger (1909) found that free transplants of periosteum caused regeneration of bone in a fair proportion of cases.

Zondek (1900), after a study of experimental fractures in mice, attributed an osteogenic function to the periosteum in the formation of callus.

Janeway (1910) reported on bone grafts in man. The implanted bone dies, he said, but is replaced by the periosteum and marrow, which live.

Pochhammer (1911) stated that the periosteum produces cartilage and bone after fracture.

Carrel (1912), working on dogs, found that periosteum transplanted under the skin produced bone.

Trinci (1912) stated that transplanted periosteum is capable of causing early regeneration of bone.

Jokoi (1912) produced new bone in six of ten cases by injecting beneath the skin or into the muscles an emulsion of periosteum of the tibias of young dogs.

Haas (1913) demonstrated that regeneration of bone is not dependent solely on the presence of preexisting bone. Regeneration of bone was never found, however, except when periosteum was present.

Schepelmann (1913) said that periosteum when transplanted into the omentum, mesentery, liver and other organs caused growth of persistent new bone. It is important, he stated, to preserve vascularity and the integrity of the cell and to use the entire periosteum.

Oechsner (1914) stated that after the placing of bone grafts in defects the periosteum causes regeneration of complete shafts of bone.

Mayer and Wehner (1914), in experiments on animals, found that transplanted periosteum produced new bone. Adult bone cells demonstrated no proliferative ability. "Most of the bone cells of the transplant eventually die," they wrote, "though frequently the graft is revascularized sufficiently early to preserve some of the bone cells. New bone growth is dependent upon activity of the periosteum and the endosteum."

Haas (1914) wrote: "It is apparent that the periosteum is very actively concerned in the regeneration of bone."

McWilliams (1914) stated that in some cases transplanted periosteum produces new bone. The life of the graft is dependent on a sufficient blood supply. Transplantation of periosteum with the bone insures an adequate blood supply.

Todyo (1917), in experiments on dogs, found that many of the components of the graft survived, particularly the periosteal and subperiosteal tissues. "The periosteum will actively form new bone," he wrote.

Berg and Thalhimer (1918) wrote: "Fully developed bone cells, in the accepted sense of the term, that is, cells within well calcified lacunae, have never been shown by microscopic observation to have divided and formed new bone." Other views of these investigators were as follows: The periosteum of a living autogenous graft remains alive after transplantation, and thereby the life of the transplanted bone is maintained. Periosteum devoid of adherent bone cells, when transplanted into foreign tissue, produces bone. Endosteum and osteoblasts lining the haversian canals in bone transplants produce bone very actively. The cambium layer, when adherent to transplanted cortex, produces bone.

Mayer (1919) wrote: "The fully developed bone cell has no power of division and bone growth results from the activity of cells lying between the bone and outer layers of the periosteum."

From a report of Delangenière and Lewin (1920) the following statement is quoted: "One can be certain that a layer of bone, with its periosteum, produces new bone and that this bone gradually grows and replaces lost bone."

Todd (1920) expressed the following belief: "Cancellous tissue (endosteum) is one of the chief agents in regeneration of bone, and, like the cambium layer of the periosteum, should be treated conservatively at operation. Compact bone plays a very minor part in regeneration."

Simon (1922) stated that living autoplastic bone with periosteum is the ideal graft, since the periosteum aids in proliferation and revascularization of new bone.

Kolodny (1923) wrote: "An adequate blood supply of the periosteum is essential for normal union of fractures. The periosteal callus plays a far greater rôle in union of fractures than the endosteal callus."

2. *All of the transplanted bone dies and is replaced by proliferation of new bone from the surrounding host tissue.* Barth (1893), in transplanting bone to trephine holes in the skulls of dogs, found that all the elements of the graft died and were absorbed and that new bone proliferated from the surrounding living bone. The final success in grafting depended largely on intimate contact between the graft and the living vascular bone. The periosteum, cortex and marrow died, and all the bone acted at first like a foreign body. The graft was gradually replaced by new-formed bone from the adjacent bone-producing tissue. This is the process called "creeping replacement." (In 1908, Barth repudiated this idea and came to believe that the periosteum was the necessary element in the life of a graft.)

Marchand (1901) stated that bone is replaced by proliferation into the necrotic substance of young bone cells from the surrounding cortex.

Grekoff and Frangenheim (1901) maintained that the source of newly formed bone is in the osseous matrix of the bed into which the bone is transplanted.

The view of Murphy (1912) was that the transplanted bone forms a scaffold for the haversian vessels from both ends of the living bone to pass over, forming a callus. Transplanted bone is only osteoconductive. It must be in contact with fresh, living bone if proliferation is desired and complete resorption is to be prevented.

Gallie (1914) transplanted bone without periosteum in dogs. The bone grafts died and were revascularized. Dead bone was resorbed and new bone produced by the bone cells, which invaded the grafts along the route of the new vessels.

Brown and Brown (1915) stated that all transplants are ultimately absorbed. The periosteum seems to have little influence on the early establishment of a blood supply.

Ely (1919) wrote: "Three things are necessary for bone formation: 1. Blood vessels. 2. Loose meshed fibrous tissue, a homogeneous matrix of granular or necrotic material. 3. A stimulus, physiological or pathological, as the case may be. . . . It is seen therefore that neither periosteum nor marrow is necessary for bone formation and that neither of them forms bone, in the proper meaning of the word."

Gallie and Robertson (1919) said that when bone is transplanted, the cells on the surface or in the haversian canals may live and proliferate; the remainder die and are absorbed. New bone proliferates on the periosteal and endosteal surfaces of the graft.

Ely (1924) stated that when a piece of bone is transplanted to the soft tissues of an animal, the bone and its marrow die; soon vascularization of the marrow begins, and shortly thereafter, formation of bone.

3. *Replacement of bone grafts and repair of bony defects are effected by proliferation of bone from the periosteum and the endosteum.* Radzimowsky (1891) said that when living, periosteum-covered bone is transplanted, the bone tissue proper dies, but the periosteum lives and produces new bone, which is deposited not only on the surface of the transplanted dead bone but in its lacunae and in the enlarged haversian canals.

Bonome (1885), in studying fractures in rats, found that bone in the immediate vicinity of the fracture died. His belief was that it was resorbed and replaced by new bone which was formed from the osteogenic layer of the periosteum.

Nichols (1904) stated that repair of a bony defect occurs by proliferation of epithelioid cells from the periosteum, accompanied by blood vessels, and by proliferation from the layer of cells lining the inner surface of the cortex (endosteum). The cortical bone seems to have a very limited or no power of proliferation.

Axhausen (1908) performed and reported in detail 146 experiments on animals with many different types of grafts. He wrote: "There is marked cellular proliferation under the periosteum, also the marrow showed proliferation, absorption and production of new bone under the periosteum, by proliferation from the endosteum, and around the new vessels which penetrate the dead bone. . . . The chief source of the young bone which replaces the necrotic bone of the transplant is the periosteum, next in order comes the marrow and endosteum."

Läwen (1908) for removal of a malignant growth resected the upper end of the humerus of a boy, aged 8 years, and replaced it with a graft from the tibia. The arm was amputated eleven weeks later owing to recurrence of the growth. The graft was richly vascular, and bone cells were resorbed. There was marked periosteal and endosteal proliferation, and new bone was forming around the new vessels.

Lobenhoffer (1910) expressed the belief that in a transplant with periosteum the cortical bone dies and is absorbed and the periosteum remains viable and produces new bone.

Albee (1913) wrote: "It is believed that periosteum and marrow substance on the bone graft serve an important rôle in aiding to establish an early and more abundant blood supply from the recipient bone to the transplant. . . . It seems very probable that the amount of haversian blood supply is in a very large degree, if not wholly responsible in determining whether the bone graft lives as such or acts as an osteoconductive scaffold."

Lexer (1908) stated that the bony tissue of a transplant is gradually absorbed and is replaced by bone which is formed from the periosteum chiefly and from the medulla in part, and that the periosteum also aids in cementing the graft to the wound and in stimulating capillary invasion and early nutrition.

McWilliams (1914) expressed himself as follows: "The living graft should be transplanted always with the periosteum on it. This is most important. . . . It seems probable that the influence of the periosteum is exerted in maintaining the nutrition of the graft."

Phemister (1914) wrote: "Osteogenesis in bone repair occurs from the inner layer of the periosteum, from the endosteum, and to a much less extent from bone cells and fibrous contents of the haversian canals." He stated, furthermore, that the viability of a transplant depends on the ability to secure nourishment; therefore, the outer cells survive and proliferate.

McWilliams (1914) again wrote: "The periosteum survives because of its sufficient blood supply from the surrounding tissues. Its inner surface forms osteoblasts which themselves proceed to reform the bone of the graft, in the event that the osteoblasts within this have died from a deficient blood supply."

The following passage is quoted from Albee (1914): "The endosteum, marrow substance and periosteum should be included on the graft, as they play a most important rôle in aiding to establish an early and sufficient blood supply from the recipient tissues to the cortical part of the graft. The endosteum is also actively osteogenetic as well as the inner layer of the true periosteum."

Haas (1914) expressed the following view: "The periosteum is directly and actively concerned in the regeneration of bone. The regeneration of bone also takes place from the marrow but to a more limited degree."

Gill (1915) transplanted entire metatarsal bones in dogs and noted good healing in most cases, with little necrosis of bone. He stated: "Revascularization of a graft takes place early and first reaches the exterior—the most vital portion of the graft."

Brooks (1917) wrote: "The living bone transplanted with the periosteum and endosteum is the only type of implant which has osteogenetic properties. . . . Osteogenesis is from the junction of the periosteum and cortical bone rather than from either alone."

Nathan (1921) expressed his belief as follows: "Bone is produced solely by osteoblasts. The osteoblasts are always confined to the cambium layer of the periosteum or the endosteum. The osteoblasts are also found in the bone marrow." Bone grafts, he said, should include the periosteum and the endosteum.

Albee (1923) said that most of the blood supply to a graft is derived from the marrow and that an early blood supply is essential to the life of a graft.

Klinkerfuss (1924) wrote: "Solid bone grafts in the main die, are absorbed and replaced by new bone tissue resulting from the proliferating of osteoblasts of the periosteum, endosteum and haversian canals."

Haas (1924) stated: "The chief source of osteogenic cells, for the repair of a fracture in a transplanted bone, is from the osteoblasts of the periosteum and the endosteum. The presence of either is sufficient for union. The periosteum plays a relatively more active part than the endosteum."

Rohde (1925) expressed himself as follows: "Cortex denuded of periosteum and marrow and endosteum does not take part in bone formation. . . . Bone-building power is found only in specific bone-building tissues (osteoblasts of the periosteum and marrow endosteum)."

Kartaschew (1930) stated that the periosteum and the endosteum are important in transplanting bone. Small chips of bone permit circulation to reach the haversian canals earlier and aid the endosteal proliferation.

Haldeman (1932) said that the periosteum plays the chief part in the healing of fractures. Endosteal (medullary) callus aids in the healing of fractures but in the absence of periosteum is often unable to complete the union.

4. *The periosteum has no osteogenetic function. Bone grows and repairs itself by proliferation of the bone chips.* Havers (1692) studied the microscopic structure of bone and determined that the periosteum is merely a connective tissue, a limiting membrane which vascularizes the bone.

Macewen (1912) said that the bone cells of the cortex, occupying the lacunae of the bony substance itself, are the active agents in the life and regeneration of a transplant. The periosteum is only a limiting membrane and takes no part in osteogenesis. The periosteum acts merely as a "limiting membrane to the osteoblasts issuing from the interior of the bone. . . . The vegetative capacity of the bone cell is fully as great as that of the epithelial cell." The periosteum is the medium through which the bone gains some of its blood supply, but it is not indispensable. Many cases have been reported in which subperiosteal resections of bone were made and in which there was no replacement by bony tissue. Diaphyseal bone is reproduced by the proliferation of osteoblasts derived from pre-existing osseous tissue. Regeneration takes place independently. "The periosteum plays no part in the reproduction of bone after transplantation."

Geddes (1912) wrote: "Bone derives from the ectoderm and not from mesoderm. Osteoblasts arise from the cells of the ectoderm and migrate as individuals to the sites of bone formation, passing through the periosteum en route. Periosteum, far from being an osteogenetic membrane, is a limiter of bone formation."

McWilliams (1912), in using ribs in experimental transplants, found that the periosteum seemed to hinder the early development of a blood supply. It served no osteogenic function.

Vogt, after subperiosteal resection of the shaft of a humerus, found no evidence of regeneration of bone.

Gallie and Robertson (1914) studied the healing of defects produced in bones of young and old animals. The periosteum, they thought, is merely a fibrous membrane without osteogenic function, and osteogenesis appears to be solely a property of the endosteum and to be as energetic in the absence as in the presence of the periosteum.

Bancroft (1914) made studies on the healing of experimental defects in bone. He wrote: "The periosteum acts as a limiting membrane to bone, tends to conserve its shape and to furnish its blood supply." Small pieces of transplanted bone grow without the aid of periosteum.

Moore and Corbett (1914), in experimental transplantation of bone in animals, found that fascia is a suitable substitute for periosteum. "Periosteum is not an essential element in the healing of bone," they stated.

Cohn (1914) wrote: "We believe that small bony transplants are osteogenetic and not essentially osteoconductive. The periosteum has no osteogenetic function, but is rather a limiting membrane. Periosteum is not essential to the repair of defects in bone."

Lewis (1914), after clinical observations, concluded that gaps in bone are filled by growth from the ends of the divided shaft under periosteal limitation and control.

Groves (1914 and 1917) expressed the belief that the periosteum is the product and not the mother of bone. All the osteogenic properties of the periosteum are due to the more or less accidental presence of the outer layer of bone cells adherent to its deep surface. Living bone is the chief source and origin of callus, which grows mainly from its outer or periosteal surface. The periosteum is chiefly a limiting membrane of the bone. The dense bone can live, grow, undergo repair and produce fresh periosteum after the periosteum has been removed.

Davis and Hunnicutt (1915), after experiments on dogs and rabbits, concluded that periosteum alone (even when osteoblasts are demonstrated) does not produce bone when transplanted. Periosteum with bone shavings attached produces new bone, they said. Particles of bone and accompanying osteoblasts are necessary for the production of bone. Periosteal flaps when attached by pedicle to the bone still do not produce bone. The nourishment of bone is in no way affected by the stripping off of the periosteum. The periosteum acts as a limiting membrane. Growth of bone into defects is from the shaft itself.

Cohn and Mann (1916) stated that the periosteum is a source of added blood supply and a limiting membrane. The endosteum and the cortical osteoblasts lying under the periosteum are the sources of formation of callus. Transplants are usually absorbed.

Dobrowolskaja (1916) cultured, incubated and studied small pieces of bone of animals. There was definite evidence of proliferation from the detached pieces of cortical bone. He expressed the belief that when the bone is transplanted with its periosteum the growth is evidently more active.

5. *New bone is formed by metaplasia of the preexisting connective tissue in the region where it is to be laid down.* Von Haller (1766) wrote: "We cannot yet distinguish the bones themselves of which the first appearance is mucus. . . . Thus the muscles, by their action, draw out the processes from the bone, and dilate the small cavities into large cells; and likewise incurvate the bones and variously modify their shape. . . . The bones at first are soft and of a mucous nature; then they acquire the consistence of jelly; and this afterwards becomes a cartilage, without any change of parts, as far as can be observed. Cartilage however is not so imperceptibly converted into bone. It never happens without the red blood making a passage for itself into the vessels of the bones. Round these vessels are formed cellular texture and laminae, which the vessels themselves seem to compress into a medullary tube. . . . But even a bony callus never becomes sound till newly formed red vessels have penetrated its substance. . . . The periosteum covers the bones as membranes the viscera . . . nor does the periosteum at all adhere to the bone, except in the epiphysis."

Hunter (1786) wrote as follows: "Bones receive most of their nourishment from the surrounding parts, as from the periosteum. . . . Bones grow by two processes going on at the same time and assisting each other; the arteries bring the supplies to the bone for its increase; the absorbents at the same time are employed in removing portions of the old bone, so as to give to the new proper form."

Blessig (1859) observed calcification of the kidneys of rabbits killed from four to six days after ligation of the left renal artery.

Paul (1886) stated that senile degeneration of arteries presents three steps: (1) calcareous degeneration; (2) irritation about these plates from fracture or other injury, leading to inflammatory proliferation; (3) ossification in this young, proliferating tissue.

Barth (1895) placed a piece of incinerated bone in the peritoneal cavity of a cat. Six weeks later he found it penetrated by connective tissue and in several places by true bone lined by osteoblasts.

Pollack (1901), in examining lungs obtained at one hundred postmortem examinations, was able to demonstrate the presence of osseous nodules in sixteen cases. He expressed the belief that old scar tissue forms osteoid tissue and bone by metaplasia.

Sacerdotti and Frattin (1902) found bone plaques in the kidneys of three of four rabbits of which the renal vessels were ligated. In two cases the ureters were tied. True cortex, periosteum and endosteum were present.

Poscharissky (1905) produced bone in a rabbit's kidney in from three to four months by ligating the vessels.

Maximow (1906) found bone as early as five weeks after ligation of the renal pedicle.

Lick (1906) ligated the renal vessels of sixteen rabbits. In four he ligated the ureter as well as the vascular pedicle. He concluded that the necessary requirement for formation of bone is young connective tissue near deposits of calcium.

Bunting (1906), after studying sclerotic aortas, wrote: "The factors in metaplastic bone formation in vessels are extensive sclerosis with the presence of calcium deposits, traumatic or inflammatory disturbance in the calcified area, with penetration by granulation tissue and the formation of bone."

Harvey (1907) applied irritants to the wall of the aortas of rabbits to induce degeneration. Bone, haversian canals and marrow were formed, and Harvey stated: "New bone formation commences in areas previously necrotic. This process of new bone formation is one of metaplasia of connective tissue."

Buerger and Oppenheimer (1908) expressed their views as follows: "It is generally conceded that the presence of lime and young connective tissue is essential to heteroplastic bone formation. Due to some stimulus, vessels penetrate the diseased mediae, young connective tissue proliferates and comes in contact with lime deposits. True bone is formed."

Pearce (1909) wrote: "True bone was found in the scar tissue of the kidney in six animals. Bone formation occurred as thin lamellae in the scar tissue immediately beneath the mucosa of the pelvis."

Baschkirzew and Petrow (1912), on the basis of experiments on animals and of clinical observation, elaborated the theory that regeneration of bone takes place by metaplasia from the surrounding connective tissue cells. The majority of bone transplants soon die; then young connective tissue cells penetrate into the vascular and haversian canals and are converted into osteoblasts and bone cells. Preservation of the periosteum is not essential to the life of the transplant, but it evidently is useful in causing more rapid union between the transplant and the surrounding tissues, in hindering resorption of the transplant and in giving the first impulse to formation of new bone.

Todd (1912) wrote: "Osteoblasts do not enter skeletal tissue along the blood vessel tracks, but are fibroblasts or connective tissue cells which have undergone certain characteristic modifications and may or may not have passed through a chondroblast stage."

Strauss (1914) made ureters experimentally from the abdominal wall. Bone formed in the layer of the fascia transversalis. No degenerative changes had taken place where bone was formed. The bone that had formed closely resembled normal bone.

McWilliams (1914) stated: "Connective tissue seems to be essential in the formation of bone. Osteoblasts are indistinguishable from fibroblasts. The first occurrence in bone formation is the arranging of fibroblasts (osteoblasts) around a blood vessel. In this new fibrous tissue calcium is deposited by some unknown influence, which goes on to the formation of bone. . . . There is some other factor making for the life of grafts than the periosteum or contact with living bone; and this I take to be a sufficient blood supply."

Moschcowitz (1916) reported several cases of calcification or ossification in the ovary. "Blood vessels, osteoblasts, bone cells, and marrow (in large part at least) are merely differentiations of the mesenchymal cell unit," he wrote.

Neuhof (1917) wrote: "In fascial transplants into experimental defects in the urinary bladder, macroscopic plaques of true bone appeared. . . . That previous bone or periosteum is not necessary for the formation of new osseous tissue was, of course, demonstrated by finding such tissue developed in situations far removed from the skeletal system. . . . The periosteum-like layer ensheathing the bone plaques can be accounted for satisfactorily on the theory of metaplasia of adjoining connective tissue and similarly, metaplastic changes in connective tissue included between the bone trabeculae will explain the development of bone marrow."

Asami and Dock (1920) ligated renal vessels and ureters of rabbits, and bone plaques formed later. Young fibroblasts accumulated to form a membrane-lined structure. Formation of bone began in the loose vascular connective tissue, close under the transitional epithelium of the calices.

Phemister (1923) found that in fascial transplants to the bladders of dogs (the urine of which is always acid) bone always formed. In similar transplants in rabbits and sheep (the urine of which is alkaline) there was no calcification or ossification. Lime salts were deposited from the lymph or blood in the portion of the transplant bordering on the lumen, where nutritional conditions were poorest, necrosis was greatest and the acidity was increased by contact with the acid urine of the bladder.

Leriche and Policard (1926) stated: "1. The formation of bone is the result of a metaplastic change in the connective fundamental substance. This metaplasia takes place in three stages: (a) transformation of the connective tissue by an edematous infiltration with a multiplication of connective fibrils; (b) infiltration by a special substance, chemically undefined—the preosseous substance; (c) deposits in that substance of a calcareous mixture of calcium phosphates and carbonafes.

"2. Osseous metaplasia can occur in all types of connective tissue; embryonal type, fibrous type, etc. The numerous forms of osseous tissue, as found among man and animals, are the result of that process.

"3. In osseous metaplasia, the cells do not play the part classically attributed to them, that is to say the osteoblasts do not secrete directly osseous substance between the cells. Such a conception is erroneous. The osseous transformation of connective tissue is a phenomenon independent of all cellular action. It is an interstitial and humoral process. . . . The periosteum is modified (to an embryonal state) by a change of circulation or by edema; it becomes then a ground for ossification. It is passively ossified—it does not make bone in an active manner."

Osseous metaplasia of connective tissue is a reversible process. Bone appears and disappears with the greatest facility. There is a continual state of unfixed equilibrium.

In transplantation of bone the formation of new bone depends on the resorption of the transplant. It seems that as a result of rarefaction of bone there is produced a localized oversupply of calcium, which provokes an osseous metaplasia in the surrounding connective tissue.

"The resorption of bone is specially directed by humoral phenomena, dependent on the circulatory activity in the bone."

Keith (1927) stated that many cases have been reported in which bone formed in the scars left by laparotomy. Osteoblasts, which are directly concerned in the formation of bone, are probably not transported by the blood stream. Fibrous tissue anywhere can produce bone if it reverts to embryologic fibroblasts (embryonal state) or edematous fibrils and if calcium is present. As the arteries proliferate, lamellae of bone appear around them. The cells which assume a bone-forming rôle are derived from the endothelium of the capillary system or from the reticulo-endothelium. Perhaps the action of an enzyme is necessary to stimulate this proliferation.

Huggins (1931) found that when the urine has been diverted from the bladder of the dog, bone still forms in a fascial transplant to the wall of the bladder. The bone forms only in the transplant, and the newly formed epithelium of the transplant is the essential factor in the osteogenesis.

Abbott and Goodwin (1932) stated that the mucous membrane of a dog's bladder when transplanted into muscle forms an epithelium-lined cyst wherein new bone is deposited after twenty days.

PURPOSE AND METHOD OF EXPERIMENTS

The presentation of such a time-worn subject as experimental transplantation of bone can be justified only if some different type of experimentation has been employed. Our efforts have been particularly along two lines. Our first purpose was to determine what difference, if any, could be noted in the rate and the type of healing of grafts taken from bone of different regions or different structures: (1) cortical bone of the tibia, (2) cancellous bone of the tibia, (3) spongy bone of the ilium, (4) periosteum and (5) chips of bone elevated in situ along the spinal column, as in the Hibbs fusion operation. Our second purpose was to determine what, if any, effect on the rate and the type of healing could be produced by "decalcification" of experimental animals.

Adult dogs were selected for all the experiments. The animals were in excellent condition. The dog's spinal column is not unlike that of man and is easily used for bone-grafting procedures.

The operations were performed under ether anesthesia with aseptic surgical technic. Spinous processes (usually four at a time) were exposed, and the dissection was carried down along the laminae, exposing them as far as possible, even to the articular facets. Bone grafts were then taken from the tibias, the entire thickness of the cortex being used. These grafts were divided into periosteal, cortical and endosteal or cancellous portions, and each of these portions was used as a transplant to the prepared bed along the spine, each being placed in a separate

portion of the prepared bed. In addition, a portion of the posterior crest of the ilium, including the posterior superior spine, was removed and used as a transplant. Thus, four separate pieces, three of bone and one of periosteum, were used in each operation, and each was placed in a separate part of the prepared bed along the spinal column.

Up to this point two animals had been used, and the same operation performed on each. After approximately thirty days the same procedure was repeated on each animal in another part of the spine. Thus in each animal we had two operative areas, so that there were four operative experiments. In addition, we carried out the Hibbs operation on two pairs of animals. This operation also was done twice on each animal at an interval of approximately thirty days. All of these experiments were repeated a like number of times on our four decalcified animals. Thus we were able to compare the amount of formation of new bone about the various types of transplants. The animals were killed approximately three months after the first operation; therefore, we had comparative data on transplants made two and three months previously.

All the animals were treated with sodium alizarine sulphonate (alizarine red) after the first operation in order to obtain vital staining of the specimens. This substance was used after the manner described by Bauer, Aub and Albright.

After each dog had been killed, the entire spinal column was removed. Sections were taken for microscopic study from each of the regions where a graft was placed. The remainder of the spinal column in most instances was macerated (in a solution of potassium carbonate 30 Gm. and sodium sulphide 15 Gm. for each liter of water) in order to get rid of the soft tissue and to allow the changes in the bone itself to be observed.

Roentgenograms were taken in most instances sixty and ninety days after the first operation. Studies of these roentgenograms in comparison with the specimens will be presented.

Microscopic sections of the regions of operation, showing the behavior of the different types of grafts, have been made. The picture differed both as to the length of time in situ and as to the type of graft. The calcium balance of the dogs also differed. Comparative study of these sections offered some interesting facts.

In order to study the effect of a decreased calcium content in the dog, certain animals were given diets low in calcium, composed of boiled rice, fish, distilled water and ammonium chloride. This regimen was continued for approximately thirty days before the first operation was performed. The diet was maintained up to the time of the first operation, after which a normal diet was resumed. By this means, some degree of decreased or negative calcium balance could be obtained. It is our belief that this decrease could be carried much further, with perhaps a more striking effect on the behavior of the transplants.

STUDY OF SPECIMENS

The study of the gross specimens revealed in all instances except two solid union between the bone graft and the bone of the host. The periosteal grafts, however, gave no evidence of formation of new bone. In the two instances in which grafts were not united and there was little or no evidence of formation of new bone, there were infected wounds. In all instances except these two, the wounds had healed solidly and there was no evidence of infection. It should be noted that no type of fixa-

tion was used in any of these cases. This simplified very much the handling of the experimental animals, and it is hard to see that the results to be described were in any way affected.

The effect of the sodium alizarine sulphonate was easily noted in all cases. Not only the newly formed bone but the surrounding bony structure, wherever it had been touched by the operative procedure, was stained bright red. Thus the spine and the tibias as well seemed to be stained as far back as the soft tissues had been reflected at the time of the operation. No difference could be noted in the different types of transplants, nor could any appreciable difference be made out between transplants in normal and those in decalcified animals, so far as the amount of vital staining was concerned. The staining of the new bone deposited was vivid in most instances.

In the study of the microscopic sections, much more accurate information regarding the relative stages of formation of new bone was gained. A description of these changes follows.

Cortical Grafts.—There was a definite tendency toward diminished condensation of the transplanted bone. However, in none of our cases was there what might be called complete death of the graft, or anything approaching it. The grafts gave evidence of union in most instances, but at the end of three months union was not so extensive as in the grafts taken from cancellous bone. The type of new bone formed in the decalcified animals seemed much more "active"; that is, this bone was in most instances made up of chondro-osteoid tissue which was rapidly turning into bone (figs. 1 and 2), whereas the tissue binding the cortical grafts to the spinous processes in the animals that were not decalcified was firm connective tissue, not giving evidence of much actual formation of new bone (fig. 3). In spite of this, in all instances but one gross examination of the specimens disclosed firm union between the graft and the host, apparently with laying down of new bone, or at least with deposition of calcium in the tissues connecting the graft to the host, as demonstrated by the presence of the alizarine red in the tissue.

Grafts from Cancellous Bone of the Tibia.—These transplants were taken from the tibial grafts; that is, the endosteal or cancellous portion of each tibial graft was removed and implanted along the laminae as a separate graft. On gross examination all of these grafts except one were well united, and all were well stained. In the microscopic sections the appearance was so similar to that shown by the grafts taken from the cancellous bone of the iliac crest that one description will suffice.

Grafts from the Crest of the Ilium.—These grafts were cut with an osteotome from a point 1 cm. below the posterior superior spine, and

ran forward along the crest of the ilium for from 3 to 4 cm. Such a graft is almost pure cancellous bone, although it is a much heavier type of cancellous bone, with its trabeculae more closely spaced, than that seen in the endosteum of the tibia. That is, the individual trabeculae

Fig. 1.—Section from a decalcified animal sixty-one days after operation. In the cortical graft (*a*) the vascular spaces are of increased size because of decalcification. The view of area *b* under higher power magnification shown at the left below gives marked evidence of formation of chondro-osteoid tissue. The cancellous graft (*b*) shows similar changes, with active formation of chondro-osteoid tissue. A view of the area *b* under higher power magnification is seen at the right below.

of the iliac crest, although no larger than those of the tibia, are more numerous and more closely packed together, giving the appearance that the bone is much heavier. The union between these grafts and the

spinous processes and laminae was without exception the best that occurred with any type of graft (figs. 3 and 4). In many instances, new bony trabeculae had formed in sixty days or less, and the grafts seemed solidly united to the bone of the host. The trabeculae were

Fig. 2.—Section from a decalcified animal eighty-two days after operation. The cortical graft (*a*) is shown at a later stage than that represented in figure 1. There is less evidence of osteoporosis. The tissue connecting the graft to the host is more advanced bone. A view of area *a* under higher power magnification is seen at the left below. The bed of the periosteal graft (*b*) shows no formation of new bone. A view of area *b* under higher power magnification is seen at the right below. The spinous process of the host is designated by *c*.

numerous and firmly bound to the spinous processes and laminae. On gross examination this was easily demonstrable, and the microscopic appearance seemed to bear it out.
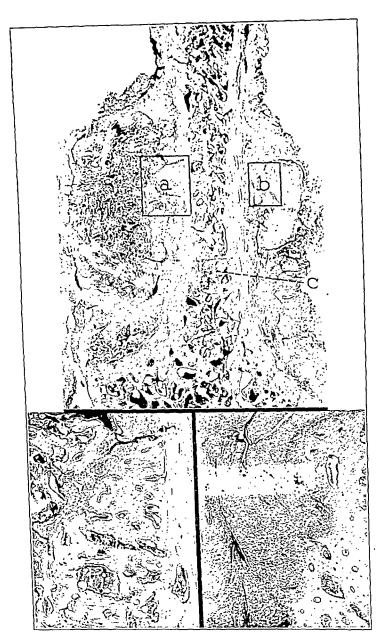
Fig. 3.—Section from a normal animal eighty-eight days after operation. There is firm bony union between the cancellous graft (*a*) and the bone of the host. A view of area *a* under higher power magnification is seen at the left below. The cortical graft (*b*) shows only fibrous union with the bone of the host. A view of area *b* under higher power magnification is seen at the right below. The spinous process of the host is designated by *c*.

Grafts of Periosteum.—In none of our experiments did the transplantation of periosteum seem to result in formation of new bone, either from the transplant or from the host tissues (figs. 2 and 4). Before too much importance is placed on this finding, however, it must be remem-
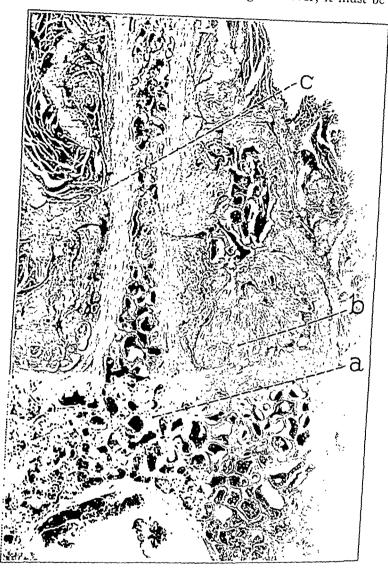
Fig. 4.—Section from a normal animal fifty-six days after operation. The spinous process of the host is designated by *a*. The cancellous graft (*b*) is united to the bone of the host by trabeculae of completely formed bone. The region (*c*) where the periosteal graft was implanted gives no evidence of formation of new bone.

bered that none of our animals was young. The periosteal transplant in all cases was obtained from the front of the tibia from which the graft was removed. In most instances it consisted of a thin piece of fibrous

tissue, without much blood supply, which separated easily from the tibia. It differed much more markedly from the periosteum of young animals than the periosteum of the tibia of an adult person differs from that of a young or adolescent person. It is our feeling, and this is cor-

Fig. 5.—Section from a decalcified animal sixty-two days after a Hibbs operation. The spinous process of the host is designated by *a*, and a chip of bone with no formation of new bone by *b*. There is some foreign body reaction (*c*) between the chip of bone and the host.

roborated by many writers, that the periosteum of a young person under certain conditions may stimulate formation of new bone but that the periosteum of older persons, at least on the shafts of the long bones where no muscular attachments are found. is a thin, almost nonfunctioning. ligamentous substance.

Bone Chips.—Experiments with bone chips were performed to determine what, if any, comparison could be drawn between the osteogenesis produced by operations like the Hibbs spinal fusion operation and that following operations in which bone grafts are employed. It has been demonstrated that the Hibbs operation will produce satisfactory bony fusion. However, in these experiments we were unable to demonstrate as extensive formation of new bone as occurred in the experiments with bone transplantation. Many of the chips when examined microscopically gave evidence of new bone forming around them. On the other hand, many of them failed to exhibit any evidence of formation of new bone, and in some instances there appeared to be death of some of the bone in the shaving and a foreign body reaction around it (fig. 5). In all instances, on gross examination there was fairly good staining by alizarine red but very little solid ankylosis.

PARTICULAR CONSIDERATION OF SPECIMENS FROM DECALCIFIED ANIMALS

Active reduction of the proportion of calcium in the skeleton is possible and, by the means which we used, fairly simply accomplished. Measurement of the amount of decalcification thus produced is much more difficult, and such a procedure seemed unnecessary in these experiments.

In most instances, the reduction was sufficient to allow one to detect a distinct difference from the way in which the normal bone cut at operation. We have already noted that the amount of red stain deposited in the tissues by the alizarine red in circulation was the same whether the animal was decalcified or not. On the other hand, in all cases in which satisfactory microscopic sections could be obtained, a particularly active osteogenic process seemed to be going on in the bone of the decalcified animals. This was shown either by the extensive formation of new trabeculae or by the active formation of osteoid tissue.

The chemical changes which take place must definitely affect the formation of new bone. Whether or not in the process of decalcification the tissues of the host, as well as those of the transplant, are so altered as to hasten the deposition of calcium when the way is prepared by adding more calcium to the diet we cannot state positively. The mechanism is perhaps purely circulatory, although the exact relationship of the circulation to decalcification and recalcification is as yet not understood.

It was noted in most of these specimens that decided widening of the haversian spaces had taken place in the grafts as well as in the tibias of the decalcified animals. This would be expected under the circumstances and was merely a manifestation of the changed content

of calcium. That these two processes were both influencing the formation of new bone seems more than likely. That they represent more than one chemical or physiologicochemical process is also more than likely. The atrophy of bone incidental to the entire process makes the grafts somewhat more permeable to the invasion by new blood vessels that is necessary for osseous growth. The decreased content of calcium adds somewhat to this effect, and at the same time it seems to us that it probably leaves the new bone-forming tissue, which is the basic substance of the bony framework, in a more receptive state when the increased amount of calcium is poured into the tissues from the blood stream. Aub and his co-workers have shown that the trabeculations furnish a readily available supply of calcium, that their number and size may be appreciably diminished by a process similar to that which we have used, and, conversely, that they may be readily built up by the addition of calcium to the diet. It seems reasonable to believe, therefore, that in a medium somewhat depleted of calcium salts the framework of the bone may be laid down more easily, and that when the necessary calcium salt is supplied it is more readily taken up and deposited in this framework, making new bone.

STUDY OF THE CUT EDGES OF THE BONE

We had used a motor saw, and the behavior of the cut edges of the bones from which the grafts were taken interested us. It has been suggested from time to time that the use of a motor saw impairs the osteogenic properties of the bone, either by overheating the bone and thus killing the osteoblasts or by packing the margins of the cut with bone sawdust and thus decreasing the permeability of the bone. In examining these tibias grossly at autopsy we found most of the defects (except in the two cases in which infection had taken place) to be filled with bone. Three months after the original operation the filling was complete; two months after operation, filling was not complete, but there was a remarkable amount of regeneration. Studies of sections taken through these defects disclosed solid bony union between the margin of the defect and the newly formed bone along one border. At the other border this was broken through, probably by manipulation. In some of the sections union was much less marked than in others. Although we cannot prove from these facts that there is no deleterious influence of the motor saw on the bone-forming properties of the graft, we can at least say that these properties are not consistently destroyed. Thus regeneration of bone will not be interfered with along the cut edge.

ROENTGENOGRAPHIC CHANGES

Study of roentgenograms disclosed two important facts. In the first place, there was decreased density of the grafts at a certain stage. This probably represents a stage when vascularization of the graft from the

host had been accomplished and through this increased vascular supply the density of the bone was diminished. As the vascular bed was laid down and completed, new bone replaced the old bone of the graft, and a new graft was formed, or at least what appeared to be a new graft. Such a process has been noted many times, not only clinically but in experiments on animals. In the second place (and this seems to us of considerable importance), the decreased density of the graft was appar-
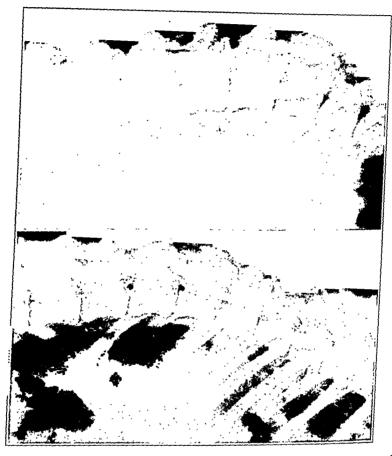
Fig. 6.—Roentgenograms of a normal animal. The film shown above was taken two months after operation. A cortical graft is seen on the right; the bone is still dense. On the left, the faint outline of a cancellous graft can be seen. The film shown below depicts the same region thirty days later. The cortical graft has undergone marked atrophy, whereas the cancellous graft shows much more plainly. It has reestablished its bony consistency.

ent much earlier in the iliac grafts than in the cortical tibial grafts (fig. 6). This indicates that the cancellous bone of the ilium was more easily infiltrated by the vascular network which invades the graft than the tibial cortical bone. Furthermore, at the stage when the cortical grafts were of diminished density (that is, at three months) the iliac grafts had reestablished their bony content, the final consistency thus being much more quickly acquired than when cortical grafts were used.

Little difference was noted between the roentgenograms of the decalcified animals and those of the normal animals. This would be expected, for it is well known that loss of lime salts from bone must be considerable to cause appreciable diminution in penetrability to roentgen rays. Roentgenograms of the tibias disclosed that repair of the defect was apparently complete at the end of three months in most instances.

<div align="center">COMMENT</div>

The classification of the theories of bone growth as outlined in this paper merely affords a working basis for comparison and cannot be regarded as rigid. As a convenience, however, it seemed to offer distinct help to us. Our own theories coincide with the more modern ones of this group; that is, that the union of grafts and probably any new formation of bone are largely due to transformation of local cells into a matrix, or basic substance, which under certain stimuli adds to itself the calcium and other salts necessary for its transformation into bone. Such a conception is simple, and we cannot elaborate it on a chemical basis. From the practical standpoint, it is to be noted that this process is apparently more easily accomplished when the transplant is of cancellous bone, probably because the cancellous bone offers a medium much more readily permeable by this matrix from the host and its calcium may be more easily mobilized and redeposited.

Besides this, we are convinced that the process of reducing the calcium content of the bone may hasten its union in a transplanted position. This may be due, again, to the fact that a decalcified graft is more readily permeable by this matrix, but we feel that an added stimulus is brought about by the chemical change of decalcification.

<div align="center">SUMMARY AND CONCLUSIONS</div>

1. Periosteal transplants in old animals do not produce new bone.

2. Cortical transplants do not completely die but unite slowly with the bone of their host, and decreased calcification is seen roentgenographically at the end of three months.

3. Cancellous bone unites more quickly and more firmly than cortical bone, whether taken from the cancellous bone of the ilium or from the endosteum of the tibia. It gives evidence of increased calcification roentgenographically at the end of three months.

4. Animals placed on a "decalcifying" diet until the time of the transplantation gave evidence of decidedly more active production of new bone both around the cortical and around the cancellous transplants.

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CHOLECYSTITIS DUE TO BACILLUS AEROGENES-CAPSULATUS

REPORT OF A CASE WITH NINE CASES FROM THE LITERATURE

IRVING GRAEF, M.D.

AND

MILLS STURTEVANT, M.D.

NEW YORK

Bacillus aerogenes-capsulatus has a wide distribution in nature. It is found in soil and sewage water and in oysters ánd other shell fish, milk, cheese and various other foodstuffs. It is present in the feces of all domestic animals and a large number of wild animals. It has been cultured from the skin of normal persons, the mouths of new-born infants, the normal salivary glands and pancreas, the normal urine and the vagina, and from the circulating blood in puerperal sepsis, chorea and typhoid fever, as well as in other diseases in which injury of the intestinal mucosa occurs. It is present in the human intestine normally, and is usually limited to the cecum and colon but is occasionally found in the small intestines. It is léss common in nursing babies and more abundant in old age. It has, however, been found in the new-born and is normally present in normal nursing infants, but it is more common in childhood and is a common inhabitant, perhaps the most abundant anaerobe, in the intestines of adults. These and other localizations of B. aerogenes-capsulatus were cited by Simonds,[1] who called attention to the high degree of natural immunity which man enjoys against this organism. He quoted Welch, who stated that there is good reason to believe that intact tissues of man in health possess marked resistance to the gas bacillus. Simonds' bibliography comprises 476 references.

B. aerogenes-capsulatus has been found in normal bile at autopsy.[2] This association was noted by Branch,[2a] who pointed out that this micro-organism, which is indigenous to areas drained by the portal system, is apparently held in abeyance by healthy living tissues. In poorly preserved bodies and during the summer months, the bacillus

1. Simonds, J. P.: Studies in Bacillus Welchii, Monograph, Rockefeller Institute for Medical Research, 1915, vol. 5.

2. (a) Branch, C. F.: A Group of Diseased Gall Bladders, New England J. Med. 201:308 (Aug. 15) 1929. (b) Gilbert and Lippmann: Zentralbl. f. Chir. 30:609, 1903.

invades and damages tissues at death, before fixation is accomplished. The presence or absence of bacteria, particularly B. aerogenes-capsulatus, in the walls and contents of normal and diseased gallbladders has been variously reported. Thus in a series of 100 cultures from gallbladders removed at operation, one series of 32 positive cultures showed no Bacillus welchii.[3] In another series[4] of 270 similar cultures, there were 58 which were positive for bacteria but showed no B. welchii. On the other hand, in 210 cases in which the gallbladder was removed at operation, Branch[2a] found B. aerogenes-capsulatus in the wall of the gallbladder in 8 cases; in the bile, in 5 cases, and in the stones, in 7 cases. It was never the predominating organism. Stolz[5] reported 3 cases of gallstones and inflammation of the biliary ducts and liver in which the gas bacillus was identified with Bacillus coli and other bacteria.

Active cholecystitis in which B. welchii has been recovered in pure culture showing a characteristic pathologic condition at postmortem examination or at operation is not often reported. In the following collection we have not included cases mentioned casually, with no criteria for diagnosis,[6] or cases in which a culture of the blood or stones yielded B. aerogenes-capsulatus even in pure culture[7] unless pure culture of the gallbladder showed the same micro-organism. We have excluded cases in which no clinical data are given, such as the cases cited in reports of the examination of gallbladders removed at operation.[8] That one must be careful in ascribing a pathologic condition to so widely distributed a micro-organism has been pointed out by Wahlberg.[9]

Recently the authors have been able personally to observe a case in which the clinical course and the postmortem observations were such

3. Johnson, W. O.: One Hundred Consecutive Cholecystectomies, Am. J. M. Sc. **170**:181 (Aug.) 1925.

4. Blalock, A.: Biliary Tract Disease, Bull. Johns Hopkins Hosp. **35**:391 (Dec.) 1924.

5. Stolz, A.: Ueber Gasbildung in den Gallenwegen, Virchows Arch. f. path. Anat. **165**:90 (July 16) 1901.

6. Andrew, E., and Hrdina, L.: Arch. Surg. **23**:201 (Aug.) 1931. Libman, E.: On Some Experiments with Blood Cultures in the Study of Bacterial Infections, Bull. Johns Hopkins Hosp. **17**:215 (July) 1906.

7. Baugher, A. H.: The Bacillus Aerogenes Capsulatus in Blood Culture with Recoveries, J. A. M. A. **62**:1153 (April 11) 1914. Greeley, H.: Idiopathic Bacillus Aerogenes Capsulatus Infection, Bull. Johns Hopkins Hosp. **29**:231 (Oct.) 1918.

8. Gordon-Taylor, G., and Whitby, L. E. H.: Bacteriological Study of 50 Cases of Cholecystectomy with Special Reference to Anaerobic Infections, Brit. J. Surg. **18**:78 (July) 1930. Branch.[2a]

9. Wahlberg, K.: Die Gasbazilleninfektion der Gallenblase, München. med. Wchnschr. **74**:2095 (Dec. 9) 1927.

as to give a characteristic picture and leave no doubt that B. aerogenes-capsulatus was the cause of a rapidly fatal cholecystitis. It is the purpose of this paper to report the case and review 9 other cases which were found in the literature.

REPORT OF CASES

CASE 1.—The first report of cholecystitis due to B. aerogenes-capsulatus was that of Cottam,[10] in 1917. The patient was a woman, aged 41, who on March 6, 1917, had a severe pain in the lower thoracic region and in the upper part of the abdomen, particularly in the midline, accompanied by vomiting. The abdomen was tender; there was no rigidity. The temperature was 98.4 F. On the following day the pain was localized at the umbilicus and McBurney's point. There was rigidity in the right lower quadrant as well as in the right upper quadrant, with general tympanites. Two days after the onset, the symptoms shifted entirely to the upper region of the abdomen. Operation was performed on this day. The gallbladder was distended and deep red. Near the fundus was a greenish, blistery, gangrenous, oval area which measured 1.5 cm. in the short, and 2.2 cm. in the long, diameter. A short distance behind this was a similar area. There were five small gallstones. The morphologic and cultural findings indicated conclusively that the organism was B. aerogenes-capsulatus.

CASE 2.—In 1922, not knowing of Cottam's case, Halle and Marquézy[11] reported what they believed to be the only case of gangrenous cholecystitis due to B. aerogenes-capsulatus. The patient, a woman, aged 60, suffered a sudden, violent pain in the right upper quadrant radiating to the right shoulder, which caused her to vomit. The pain subsided but left her weak and indisposed. Five days later, after she had taken a cathartic, the symptoms recurred. Fever and meteorism developed. On the third day of her second attack, she had jaundice, violent pain in the region of the gallbladder and respiratory signs and symptoms which confused the picture. On the fourth day, operation was performed under local anesthesia. There was no pus in the abdominal cavity, but the omentum showed fat necrosis like that in certain forms of gangrenous pancreatitis. One of the areas removed for biopsy showed a large, gram-positive anaerobe. When the biopsy specimen was macerated and injected into a guinea-pig, the animal died within ten hours, and B. aerogenes-capsulatus was recovered from the liver and the spleen. The patient died two days later. The gallbladder contained fluid and gas but no stones. It was ulcerated and showed gangrenous lesions. No secondary infection was apparent.

CASE 3.—During the same year, Lereboullet[12] reported briefly a case of perforating cholecystitis with fetid pus. The patient had an old biliary calculus. Death followed a "peritoneal episode comparable to that described by Halle and Marquézy." There were gangrenous perforation and peritonitis with fetid pus. The micro-organism obtained in pure culture was studied by Zuber, who found it to be B. aerogenes-capsulatus.

10. Cottam, G. G.: Gangrenous Cholecystitis with Report of a Case Due to the Gas Bacillus, Surg., Gynec. & Obst. **25**:192 (Aug.) 1917.

11. Halle and Marquézy: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:49 (Jan. 13) 1922.

12. Lereboullet: Bull. et mém. Soc. méd. d. hôp. de Paris **46**:257, 1922.

CASE 4.—In 1925, Kirchmayr [13] published what he thought to be the first case of infection of the gallbladder due to the gas bacillus. The patient, a man, aged 64, suffered an attack of cramplike abdominal pain which subsided after a few hours. Fourteen days later he was seized with sudden abdominal pain. The abdomen was distended. There were circumscribed tenderness in the right lower quadrant and marked tenderness in the region of the gallbladder. Perforation was feared. An operation was accordingly performed on the third day, following the second attack of pain. When the abdomen was opened, gas with a putrid odor escaped. The gallbladder was as large as a fist and adherent. The fundus showed irregular, delimited necroses from the size of a pinhead to more than that of a lentil. When the gallbladder was aspirated, gas and bloody bile were obtained. Attempted ligation of the neck of the gallbladder and of the cystic artery separately tore the friable tissue in both cases in such a manner that gauze packing was resorted to. The enlarged gallbladder was edematous in all layers and was so infiltrated by small gaseous vesicles that it crepitated. In many places the mucosa was necrotic. In addition to bloody, foul-smelling bile, the gallbladder contained sand with granules as large as a hempseed. The wall of the gallbladder contained multiple older abscesses of the wall, and the mucosa was discolored by parietal phlegmons. The wall showed acute phlegmonous destruction. The culture of the bile showed a gram-positive anaerobe of the Welch group in pure culture. The patient made a rapid recovery.

CASE 5.—In 1927, Gould and Whitby [14] reported the case of a woman, aged 46, who suffered severe, paroxysmal pain in the right upper quadrant for two days. The temperature, which at the onset was 99 F., rose to 101.2 F. Operation disclosed a tense, injected gallbladder with rancid contents. This was removed. There was slight uniform thickening of the walls, with injection of the coats. There was patchy gangrene of the mucosa so that the latter presented a mosaic of gangrenous areas surrounded by intensely congested but living mucosa. A smear showed large quantities of gram-positive, thick bacilli which were identified as B. welchii by injection into guinea-pigs. Six stones were found; these were crushed, and B. welchii were cultured from the inside. The patient recovered.

CASES 6 and 7.—During the same year, Wahlberg [9] published the report of a case. In this patient, a woman, 36 years old, two months following miscarriage and two days after curettage, there suddenly developed a severe pain below the right costal arch and slight jaundice with chill. A symptomatic recovery occurred, but five weeks later she presented the symptoms of sudden, acute cholecystitis with fever and vomiting. There was a tumor in the right upper region of the abdomen, extending to the umbilicus. At operation there was no evidence of infection with the gas bacillus, but the bile, the wall of the gallbladder and the excised fragments of liver showed pure cultures of the gas bacillus. It was impossible to demonstrate the bacillus in duodenal contents removed by intubation. Cultures of the blood and the urine were sterile. The patient recovered in three weeks.

Wahlberg also reported briefly a case in which the gallbladder had perforated. Pure cultures of the gas bacillus were made from a large abscess and from the bile. The patient recovered.

13. Kirchmayr, L.: Ueber einen Fall von Gasbrand der Gallenblase, Zentralbl. f. Chir. **52**:1522 (July 11) 1925.

14. Gould, E. P., and Whitby, L. E. H.: A Case of B. Welchii Cholecystitis, Brit. J. Surg. **14**:646 (April) 1927.

Case 8.—In 1929, Spitznagel [15] reported the case of a man, aged 50, who was always well until four days before he was seen, when a sudden, severe pain developed in the region of the gallbladder which subsided after a few hours. Four days later jaundice developed and he applied for treatment. On the second day, under observation, severe colic similar to the first attack developed, and he rapidly became very ill. The jaundice was intense, and the temperature rose to 39.9 C. (103.3 F.). The patient was judged too ill for operation, and in a few hours he died. Necropsy was performed sixteen hours later. The subcutaneous tissues contained gas. The skin of the entire body was like a cushion. When the abdomen was opened, gas escaped with a loud noise. The abdominal cavity contained dirty, hemorrhagic fluid. The gallbladder was markedly enlarged. The serosa was opaque and covered with fibrinous deposits. It was loosely adherent to surrounding structures, and here and there were discolored, necrotic spots. The lumen contained discolored and dirty brown bile without bubbles of gas. The mucosa was largely necrotic, containing dirty brown, friable islands. The wall was thinned, the necrotic spots forming the thinnest part. No gallstone was found. The ducts were patent. The other organs, except the gastro-intestinal tract, showed gaseous edema. Bacterial examination of bile and blood gave pure cultures of the gas bacillus; whereas other organs showed simple necrosis and gaseous edema, sections from the gallbladder showed that the mucosa was lacking or demonstrable only in the shadowy outline. The mucosa was entirely necrotic and infiltrated with gram-positive rods which were also present in the deeper layers. The capillaries of the gallbladder were congested and partially thrombosed.

Case 9.—In 1931, Hegner [16] reported a case in a man, aged 62, who three weeks before he was first seen, had an attack of pain like colic due to a gallstone. Sixteen days later the pain recurred. Slight jaundice developed, and the patient suddenly became very ill and died. From around the wall of the gallbladder and around the tumor mass B. welchii was obtained in pure culture.

Case 10.—Our patient, a man, aged 63, a native of Poland, was admitted to the Third (New York University) Medical Division of Bellevue Hospital on Jan. 18, 1932. He gave a history of having been kicked in the chest by a horse nineteen years before. After that he did not consider himself well enough to work. Five years earlier the right kidney had been removed because of blood in the urine. Fifteen years before, the right leg had been operated on for "blood poisoning."

On admission, the patient's temperature was normal, and his complaints were mainly of pediculosis vestimentorum. On examination he appeared weak and prostrated without apparent cause. The blood pressure was 170 systolic and 110 diastolic. The liver was readily palpable below the costal margin. It was not tender.

On January 20, forty-eight hours after admission, the patient had a chill, and the temperature rose to 104 F. He became cyanotic and dyspneic. The leukocyte count, which was 7,200 on admission, rose to 17,000. Prostration, dyspnea and cyanosis continued, and the patient died on January 22.

Autopsy (Performed Four Hours Post Mortem).—The body was that of an elderly white man, well developed and well nourished. The abdomen appeared distended. The regional lymph nodes were not palpably enlarged. There was no icterus.

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15. Spitznagel, K.: Gasbazillencholezystitis, Wien. med. Wchnschr. **79**:461 (March 30) 1929.

16. Hegner, C. F.: Gaseous Pericholecystitis with Cholecystitis and Cholelithiasis, Arch. Surg. **22**:993 (June) 1931.

On section the subcutaneous fat was moderate in amount. The peritoneum was smooth and glistening. There was no free fluid. There was marked gaseous distention of the intestines.

Lungs: The lungs were voluminous; the pleural surfaces were adherent by dense bands of fibrous tissues. There was about 150 cc. of straw-colored, clear fluid in each sac. On section there were no notable changes except many areas of bullous emphysema.

Heart: The pericardium was natural. No changes were visible to the naked eye on examination of the myocardium, the endocardium and the valves, with the exception of slight atheromatous changes in the aortic leaflet of the mitral valve. A small bubble of gas about 5 mm. in diameter was seen beneath the intima on the ventricular aspect of the posterior aortic cusp. The bubble ruptured on pressure,
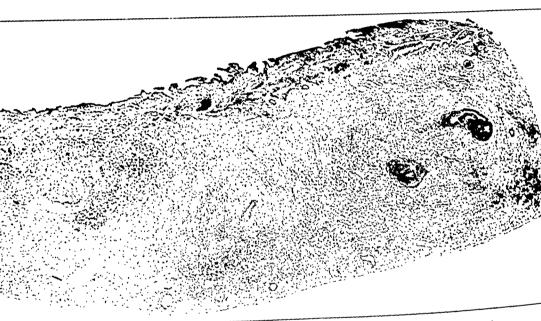
Fig. 1.—Low power photograph (Leitz Summar, 35 mm.) of a section through the wall of the gallbladder, showing the loss of lining epithelium, the thickening of all of the coats, thrombi in the vessels and abscesses.

revealing a break in the endothelial surface. The coronary arteries were sclerotic throughout.

Aorta: There was marked hemolytic staining of the intima, and a small sub-intimal hemorrhage was found in the arch of the aorta. There were numerous areas of atheroma with calcification throughout the aorta.

Gastro-Intestinal Tract: There were numerous small hemorrhages in the mucosa of the stomach. There were no ulcers. The small intestine and the large intestine showed marked dilatation. The mucosa and muscularis showed no changes.

Pancreas, Spleen and Liver: The pancreas was normal; the spleen, soft and slightly enlarged, but otherwise intact. The liver was enlarged and weighed 2,000 Gm. The capsule was smooth. On section, bile containing many gas bubbles exuded from the larger bile ducts, and numerous stones were found in all the visible biliary passages. The parenchyma of the liver was opaque, dull and grayish brown, and the markings were obscure. No areas of autolysis were visible. The

gallbladder was enlarged and markedly thickened. On palpation crepitus was made out within the gallbladder, and on section a foamy, greenish fluid escaped. The gallbladder contained many small faceted stones. When the surface was washed, numerous deep ulcerations were seen, many of which had hemorrhagic bases. The cystic and common ducts were dilated and patent. They contained stones and frothy bile.

The rest of the autopsy revealed no relevant changes.
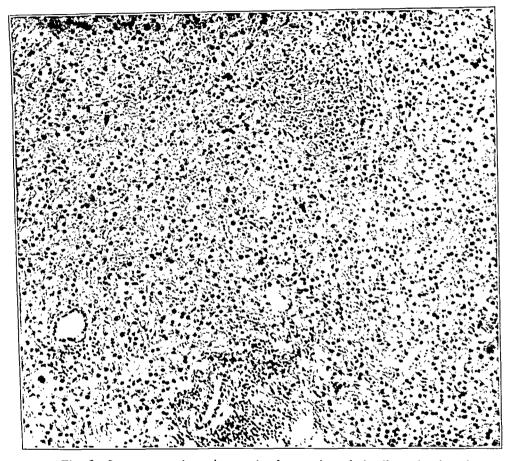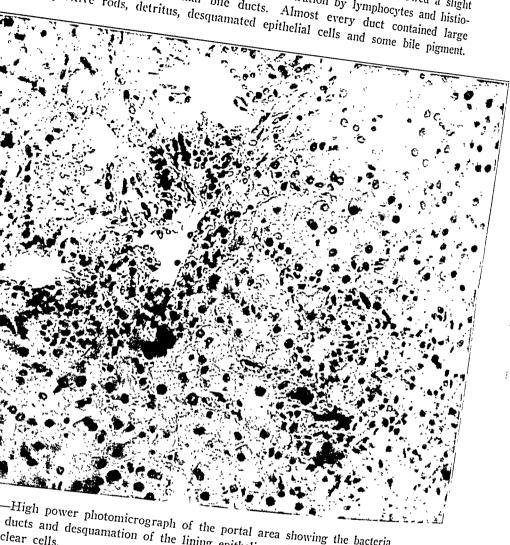
Fig. 2.—Low power photomicrograph of a section of the liver showing the low grade periportal hepatitis and, in the upper part of the field, a focus of parenchymatous degeneration.

Microscopic Report.—Gallbladder: There was marked edema of all the coats of the gallbladder. The lining epithelium was completely gone; only a few villi were recognized, and there were numerous ulcers which extended into the muscularis. There was infiltration of the coats by lymphocytes, histiocytes and polymorphonuclear leukocytes, and numerous small abscesses were seen in the wall with formation of calculus in the deeper crypts. Numerous arteries showed thrombosis, and there was edema of the vascular coats with infiltration by polymorphonuclear leukocytes.

Liver: The lobules were readily made out except in areas in which the parenchyma had been autolysed or compressed by gaseous formation. Numerous areas showed focal necrosis of the hepatic cells, some of which were central and others of which were portal in location. The cells were miliary in size and were not associated with cellular reaction. Most of the portal areas showed a slight increase in connective tissue and moderate infiltration by lymphocytes and histiocytes. There were no normal bile ducts. Almost every duct contained large gram-positive rods, detritus, desquamated epithelial cells and some bile pigment.

—High power photomicrograph of the portal area showing the bacteria ducts and desquamation of the lining epithelium. Note the infiltration clear cells.

a lymphatic channel was encountered, choked with bacteria, and an rea was found within the hepatic lobules which showed large clumps n the sinusoids. The apparently intact hepatic cells showed various slight fatty metamorphosis to karyorrhexis. The hepatic arterioles rate sclerosis, but none of them was necrotic. There was an extensive ment in all the sections examined, both in Kupffer's cells and in the entral cords. Most of the pigment was golden brown and did not

give a positive reaction for iron. Evidence of hemolysis was seen in the finding of large amounts of scattered pigment free in the sinusoids and blood channels.

Sections of the other organs showed no notable changes.

Bacteriologic Examination.—Cultures made from the gallbladder and the heart's blood at necropsy revealed B. welchii in pure growth.
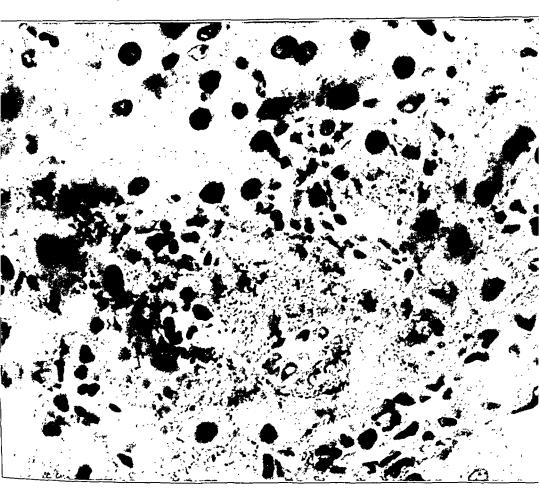
Fig. 4.—High power photomicrograph (oil immersion) showing the bacilli in the hepatic sinusoids and capillaries.

Pathologic Diagnosis.—This comprised: coronary sclerosis; atheromatosis of the aorta, with hemolytic staining of the intima; emphysema and bilateral chronic adhesive pleuritis; chronic periportal hepatitis; acute focal hepatitis with focal necrosis; acute catarrhal cholangeitis, and choledocholithiasis; acute and chronic ulcerative cholecystitis (presence of B. welchii) and cholelithiasis; septic softening of the spleen; surgical removal of the right kidney; pyelitis; local recurrent hypernephroma and compensatory hypertrophy of the left kidney.

Ten Reported Cases of Infection of the Gallbladder by B. Aerogenes Capsulatus

Author	Year	Sex	Age	History of Previous Attack	Interval of Well-Being Between Previous and Final Attack	Jaundice	Gallstones	Gangrene of Gallbladder Wall	Abscesses	Ulceration	Perforation	Outcome (Recovery or Death)
Cottam [10]	1917	F	41	None	......	......	Five small	Yes	......	...	......	Recovery
Halle and Marquézy [11]	1922	F	60	Sudden violent pain in right shoulder with vomiting	5 days	......	None	Yes	......	Yes	......	Death
Lereboullet [12]	1922	..	..	......	......	......	......	......	......	...	......	......
Kirchmayr [13]	1923	M	64	Abdominal cramplike pain	14 days	No	One	Yes	......	...	......	Recovery
Gould and Whitby [14]	1927	F	46	No	......	......	Sand, with granules the size of hempseed	Yes	Multiple in wall	Yes	Yes, with fetid pus	Death
Wahlberg [0]	1927	F	36	Severe pain below right costal arch	5 weeks	Slight	Six	Yes	......	Yes	No	Rapid recovery
	1927	..	..	......	......	......	......	Yes	......	Yes	......	Recovery
Spitznagel [15]	1929	M	50	Sudden severe pain in region of gallbladder which subsided after a few hours	4 days	Intense	......	...	......	Yes	......	Recovery
Hegner [10]	1931	M	62	Pain like colic due to gallstone	16 days	Slight	None	Yes	......	Yes	......	Death
Graef and Sturtevant	1933	M	63	None	......	0	Numerous	Yes	......	Yes	......	Death

ANALYSIS

In 10 of the reported cases of infection of the gallbladder by B. aerogenes-capsulatus, including our own case, the ages were given in 8 cases, as follows: 36, 41, 46, 50, 60, 62, 63 and 64. The average age was 52.75. Four of the patients were women and 4 men.[17] In only 1 case was there a history of biliary disease. Five patients had a preliminary attack of pain like that of colic due to gallstones, which subsided. It was followed by a secondary attack ending rapidly in death or operation. The interval between the pain and the rapidly fulminating attack was four days, five days, fourteen days, sixteen days and five weeks. It has been suggested [18] that the preliminary attack is pain due to gallstones, and that at this time injury is done to the mucosa, making invasion by the gas bacillus possible. Opposed to this theory is the fact that Halle and Marquézy's patient had no gallstones with a typical prodromal attack. Of the 10 patients, 5 recovered and 5 died.

Our patient gave no history or signs of cholelithiasis, clinically, yet from the pathologic examination we are certain that there were biliary calculi, with chronic cholecystitis and probably chronic periportal hepatitis. The dilated duct and ampulla suggested that one stone at least had passed. In the absence of a history of this event, the suspicion arises that possibly some of the history may have been withheld. During the four days of observation the patient seemed like a person who is ill from beginning pneumonia or some severe infection, but there were no localizing symptoms.

SUMMARY

Nine cases of infection due to B. aerogenes-capsulatus of the gallbladder are collected, and 1 case is added. With or without a preliminary attack of pain and a quiescent period of from four days to five weeks, the patient is seized with an overwhelming infection, which usually points to involvement of the right upper quadrant. In 2 cases it was difficult to localize. Death quickly supervened when operative relief was not given quickly. The diagnosis in the authors' case was made post mortem.

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17. In 2 cases neither age nor sex was reported.
18. Kirchmayr [13] and Wahlberg.[9]

ACUTE APPENDICITIS

A SECOND REPORT OF ONE THOUSAND CONSECUTIVE CASES

E. P. QUAIN, M.D.

The Quain and Ramstad Clinic

BISMARCK, N. D.

One thousand consecutive cases of acute appendicitis were reported by myself and Dr. Waldschmidt in 1928.[1] From September, 1927, to October, 1932, a second series of one thousand patients with the same diagnosis have been operated on by the surgeons of the Quain and Ramstad Clinic.

In studying the records in this second series, we were confronted with the same difficulties which we met in our first report, namely, the impossibility of making an accurate classification of the stages or complications of the disease found at the time of operation without the use of a long and useless list of adjectival phrases. However, our report is intended chiefly for the practical surgeon who is more interested in the welfare of his individual patients than in the details of pathologic by-products and side issues which have no vital bearing on the success or failure of treatment.

While the former classification is continued, it is not claimed to be scientifically accurate; yet we believe that it serves a very practical purpose at the time of operation in helping the surgeon to decide the two vital questions, *whether* to drain and *how* to drain.

According to our method of classification, the plan is to place in group I all cases which do not need drainage. If a drain has been inserted as a precautionary measure and later developments (a sterile culture or the absence of a local reaction) indicate its early removal, the case would still belong in group I.

Since we follow, in general, the same surgical technic in the treatment of all patients in whom the infection has gone through the appendical wall, it seems superfluous to classify cases in groups II and III. Such a classification is merely an indication of the surgeon's best opinion

Grouping of 1,000 Cases of Acute Appendicitis According to Extent of Peritoneal Infection *

	Group I	Group II	Group III
Total number of cases......................	637	212	151
Appendectomy performed....................	637	209	151
Appendectomy not performed..............	0	3	0
Died...	2	9	27
Age of patients			
Youngest..............................	2 years	2 years	21 months
Oldest..................................	58 years	78 years	73 years
Average................................	22 years	21 years	19 years
Time of operation after onset			
Shortest...............................	½ day	½ day	1 day
Longest................................	26 days	21 days	22 days
Average................................	3¼ days	4¾ days	4½ days
Duration of drainage			
Shortest...............................	1 day	1 day	½ day
Longest................................	8 days	65 days	65 days
Average (of those drained)....... ...	2 days	14 days	16½ days

Major Postoperative Complications

Group I	Group II	Group III
Secondary abdominal abscess...................... 3	Secondary abdominal abscess...................... 5	Secondary abdominal abscess...................... 6
Acute bronchitis............. 1	Multiple abscess of liver..... 1	Subphrenic abscess.......... 1
Coronary embolism......... 1	Pelvic abscess................ 2	Acute bronchitis............. 1
Enteritis...................... 1	Subphrenic abscess.......... 1	Empyema...................... 1
Postoperative hemorrhage.. 1	Acute bronchitis.............. 4	Enteritis...................... 1
Intestinal obstruction....... 2	Pulmonary embolism........ 1	Fecal fistula..................13
Acute otitis media........... 1	Fecal fistula..................10	Postoperative hemorrhage.. 3
Acute parotitis.............. 2	Postoperative hemorrhage.. 1	Influenza...................... 2
Acute progressive peritonitis................... 1	Pulmonary infarct.......... 1	Myocardial insufficiency..... 2
Phlebitis..................... 1	Acute mania................. 1	Intestinal obstruction.......31
Acute pleurisy.............. 1	Myocardial insufficiency..... 1	Acute otitis media........... 2
Pneumonia................... 3	Acute nephrosis............. 1	Acute parotitis.............. 1
Acute pyelitis............... 2	Intestinal obstruction.......24	Phlebitis..................... 1
Acute tonsilitis............. 2	Phlebitis..................... 2	Pneumonia.................... 4
Variola...................... 2	Pneumonia................... 3	Acute pyelitis............... 1
	General septicemia........... 1	General septicemia........... 1
	Acute tonsillitis............. 1	Cerebral thrombosis......... 1
		Acute tonsillitis.............. 2
		Acute uremia................ 1

Secondary Operations

Group I	Group II	Group III
Enterostomy................ 5	Enterostomy (51 primary)..84	Enterostomy (92 primary).129
Incision and drainage of abdominal abscess.......... 3	Closure of fecal fistula...... 7	Closure of fecal fistula...... 6
	Incision and drainage of abdominal abscess.......... 5	Incision and drainage of abdominal abscess.......... 6
	Gastrostomy................. 2	Gastrostomy................. 6
	Drainage of pelvic abscess... 1	Cecostomy................... 3
	Intestinal resection.......... 1	Intestinal resection.......... 2
		Thoracotomy................. 1
		Drainage of pelvic abscess... 1
		Ileocolostomy............... 1

Mortality

Group I	Group II	Group III
Coronary embolism......... 1	Multiple abscess of liver..... 1	Peritonitis and ileus.........19
Enteritis and streptococcic peritonitis................. 1	Bronchopneumonia.......... 1	Peritonitis and bronchopneumonia................. 4
	Pulmonary embolism........ 1	Peritonitis and diabetes..... 1
Total.................... 2	Postoperative hemorrhage.. 1	Peritonitis and myocardial insufficiency................. 2
(0.31%)	Ileus........................ 3	General septicemia........... 1
	Ileus and acute mania....... 1	
	General septicemia........... 1	Total....................27
		(17.8%)
	Total.................... 9	
	(4.2%)	

Average mortality in 1,000 cases .... 3.8 %
Average mortality in 2,000 cases now reported 3.25%

* Group I includes cases of infection confined to the appendix; group II, abscess, and cases with peritoneal infection restricted to the immediate neighborhood of the appendix (early stage of progressive peritonitis), and group III, cases of diffuse and progressive peritonitis.

after consideration of both the preoperative and the operative findings. It simply shows his judgment as to the degree and extent of infection at the time of operation. "Progressive" peritonitis is present on every peritoneum after contamination from a ruptured appendix. The "progress" may become limited by nature, by the surgeon or by both. The classification, although illogical, has been continued from force of habit rather than from need or from the point of view of practical service.

We are aware of certain criticisms of our previous résumé based on the fact that it did not include any pathologic reports indicating whether in the cases in question the condition was acute appendicitis. In reply, it may be stated that no case of appendicitis has been included in group I in either of the reports unless the appendix was so acutely infiltrated, thickened, distended or surrounded by recent adhesions, exudate or fibrinous deposits that any tyro in the profession could recognize it as the site of an acute infection.

Furthermore, in all the cases of appendicitis in group I (infection confined within the appendix) the appendix was sectioned and microscopically examined by a competent pathologist, and the acutely inflammatory process was verified. Cases of appendicitis usually classified as "interval (!)" were not included in either report.

In groups II and III (appendicitis with abscess or local or progressive peritonitis) microscopic sections were not made, as a rule, unless definite information was desired as to the nature and origin of the infection (tuberculosis, tumor, etc.). In the presence of a gangrenous or perforated appendix located in an abscess cavity or in free communication with an infected peritoneum, laboratory examinations are not needed as an aid in either diagnosis or treatment.

The purulent exudate produced by the colon bacillus is readily recognized by its odor. The patient's resistance, as a rule, is more likely to overcome the colon type of bacteria than the almost odorless staphylococcic and streptococcic infection. (This observation has given rise to an operating room saying to the effect that "the worse they smell, the sooner they're well.") In all doubtful cases laboratory examinations governed in determining whether free peritoneal exudate was dangerously infectious or not. In the presence of an apparently unperforated appendix with a seropurulent or fibrinous exudate cultures were always made. Smears were examined immediately, except at night, when laboratory attendants might not be available.

The method of operation was the same as that previously described. Enterostomy was performed more often than in the former series. In some cases the results were disappointing. More often it gave satisfaction, and many times it was so evidently life-saving that we do not feel justified in limiting its use, in spite of the critical attitude adopted by some eminent surgeons.

The earliest possible removal of an acutely inflamed appendix, irrespective of its "classification," seems as essential now as before. The same holds true in regard to the necessity of locating and delivering the appendix by finger touch and with the least possible retraction and disturbance of the intra-abdominal contents.

The importance of constant and experienced postoperative management may be seen in the following comparison between the mortality in the two hospitals where our patients were treated. Of the 323 patients operated on for acute appendicitis in hospital no. 1, 16 (4.9 per cent) died, while in hospital no. 2, 22 (3.2 per cent) deaths followed the same type of operation on 677 patients. There was no appreciable difference in the severity of the disease among the patients admitted to the two hospitals. The postoperative observation and treatment in hospital no. 2 are under the direction of one man, an associate surgeon of twenty years' experience, who has made a special study of the type of complications usually met with in this disease.

We can find no other reason for the decidedly higher mortality in the second series than the longer time which elapsed between the onset of the illness and the operation. Our records show that the average time between the onset and operation was more than twelve hours longer in the second series than in the first. This fact may largely be ascribed to the hard times and to a universal tendency to "wait and see" before deciding to incur the expense of medical care. In the meanwhile, various family remedies, including laxatives in liberal doses, have served to disseminate the infection.

Two patients who were admitted to the clinic with a diagnosis of acute appendicitis were in extremis and were not operated on. Several patients with severe peritonitis died within a few hours after operation.

The case histories were studied thoroughly, and the postoperative results are shown in the table, which was arranged as nearly as possible in conformity with the previous report.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

E. STARR JUDD, M.D.

ROCHESTER, MINN.

JEAN VERBRUGGE, M.D.

ANTWERP, BELGIUM

ALEXANDER B. HEPLER, M.D.

SEATTLE

ROBERT GUTIERREZ, M.D.

NEW YORK

AND

VINCENT J. O'CONOR, M.D.

CHICAGO

KIDNEY

Anomaly.—Roscher [1] reviewed malformations observed in the Norwegian University Clinic from 1914 to 1930. The material is divided into two groups: (1) cases in newly born infants (1,532 necropsies, which revealed 104 malformations, of which 40 were malformations of the kidney or urinary tract) and (2) cases in older children and in adults (3,995 necropsies, in which 104 malformations of the kidney or urinary tract were discovered).

Hydronephrosis and anomalies of the ureter were common in the first group and were associated with stricture, valvular formation and dilatation of the ureter. The author stated, however, that he found hydronephrosis and dilatation of the ureter without any associated stricture or valvular formation. It is evident from the material that hydronephrosis and dilatation of the ureter should be regarded as malformations and not merely as secondary results of stricture.

Roscher found that 9 of 11 cases of cystic kidney were associated with malformations in the urinary tract or elsewhere; this clearly indicates that cystic kidney, or at least its origin, is a malformation. In the second group, aplasia and hypoplasia of one kidney occurred in 0.75 per cent of the cases. About 50 per cent of the cases of hypoplasia were associated with hydronephrosis. The hydronephrosis was unilateral in

1. Roscher, Fredrik: Ueber die Häufigkeit, die Art und die pathogene Bedeutung von Missbildungen der Niere und der Harnwege, Acta chir. Scandinav. 70:493, 1933.

14 instances and bilateral in 14. It was generally associated with mal-formations of the ureter, such as dilatations and valvular formations; the latter, however, usually did not occasion true obstruction. Of the 28 cases in which hydronephrosis was found, 19 were cases of pyelo-nephritis and 1 a case of pyelitis. In 12 cases the pyelonephritis was the direct cause of death and in 5 cases it contributed to a fatal issue. In only 2 cases had calculi formed. In the 12 fatal cases of pyelonephritis 8 of the patients were children under 7 years of age. These children had had pyuria for a long time, and most of them died in uremia.

Cystic kidney occurred bilaterally in 7 cases and unilaterally in 2. In 1 of the latter cases hydronephrosis was present in the opposite kidney. In the other case there was aplasia of the opposite kidney.

Settergren [2] gave an account of congenital ectopia of the kidney. He stated that the symptoms vary greatly and are not specific; consequently the diagnosis as a rule causes difficulty, particularly in cases of pelvic kidney in women. Pyelography generally clinches the diagnosis. A sound ectopic kidney that does not give rise to symptoms should be let alone, whereas a diseased kidney should be removed. When a sound kidney on account of its abnormal position produces symptoms or when a kidney presents pathologic changes without an unfavorable prognosis, nephropexy should be tried.

Settergren described 6 cases of abnormal position of the kidney, in 3 of which the condition was certainly congenital and in 3 of which it was probably congenital. In 4 of the cases the ectopia was on the right side, and in 2, on the left. Five of the patients were women, and 1 was a man. In cases 1 and 2 the diagnosis was made only after exploratory laparotomy performed because an ovarian tumor was suspected. In case 1, the kidney was situated in the small pelvis, and since nephropexy could not be carried out nephrectomy was done on account of pain, although the kidney appeared to function normally. It presented inter-esting anomalies in respect to its rotatory position and vascular supply. The patient's complaints disappeared after operation. In case 2, the kidney was situated immediately above the innominate line. The patient was three months pregnant. The kidney was retained, and pregnancy and parturition proceeded in a normal manner. In case 3, on pyelog-raphy, a probably ectopic kidney was noted, situated mainly above and close to the side of the sacral promontory. The patient had earlier passed through two parturitions without any particular difficulty. The renal symptoms were so slight that operation was not indicated. In case 4, operation was not performed. The patient was a nullipara,

2. Settergen, Folke: Ectopia renis congenita. Acta chir. Scandinav. **70:**563, 1933.

aged 74. A diagnosis of congenital pelvic kidney was made by means of pyelography. In case 5, in which the patient was a multipara, the ectopic kidney, situated above the small pelvis, had occasioned severe symptoms of cystopyelitis for fifteen years. The renal pelvis was transformed into a large, convoluted, saccular 'formation filled with concretions. The patient had earlier been treated for salpingitis, but the symptoms might even then have been caused by the unsound kidney alone. A roentgenographic shadow, probably occasioned by an atypical lobe of the liver, made the diagnosis more difficult. Nephrectomy was performed. In case 6, the ectopic kidney was pyonephrotic and contained concretions. Ureteral stricture may possibly have contributed to the renal complications. The diagnosis was made with the aid of a pyelogram; nephrectomy was performed, and typical vascular anomalies were found.

Settergren gave a final account of the relation of ectopia of the kidney to pregnancy and parturition. Considering the risk of complications that may thus arise, the lines of treatment are as follows: If from the obstetric standpoint operation on a sound ectopic kidney is considered to be indicated, nephropexy should be tried, and extirpation should be carried out only in absolutely imperative and exceptional cases. At parturition the patient with an ectopic kidney should always be hospitalized, even if delivery has occurred spontaneously earlier. In cases in which an ectopic kidney is present with simultaneous renal disease, there may sometimes be indications for sterilization. A ptotic kidney which is in an acquired anomalous position constitutes, as a rule, no complication in pregnancy or parturition.

Stone.—Hellstrom [3] *reported recurrence of stones following their* removal or passage from the upper part of the urinary tract. In 147 cases operation was not performed. In 108 cases the stone was passed, and there was no recurrence. In 14 cases the stone was not removed, but no additional stones formed. In 25 cases (17 per cent) new stones formed. In 8 of the cases in which there were recurrences the stone formed on the same side; in 8, on the opposite side, and in 7, on both sides. In 2 of the cases, the site of formation was not stated. Recurrence was looked for in 233 cases in which operation was performed. In 58 (25 per cent), there was recurrence. There was a true recurrence on the same side in 19 cases, and on both sides in 7. In 12 cases, stones recurred only on the side on which operation was not performed. In 4 cases, it was impossible to state the site of recurrence. In 16 cases stones developed as a result of fragments that were left

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3. Hellstrom, John: Ueber Rezidive nach Operationen wegen Nieren-und Uretersteinen, Ztschr. f. urol. Chir. **37**:83 (April 22) 1933.

after operation. In 11 of these 16 cases multiple stones were known to be present originally; in 3 cases there was a large coralliform stone, and in 2, extensive infection was present.

Pyelolithotomy was performed in 5 cases, pyelonephrolithotomy in 3 and nephrolithotomy in 6; pyelo-ureterolithotomy and ureterolithotomy were each performed in 1 case. In 3 of the cases in which operation was performed there was extensive bilateral infection, and in 4 there were multiple oxalate stones. In 19 cases the stone recurred only on the side on which operation was performed; in 7 it recurred on the opposite side. Therefore, stones recurred in 26 cases (11 per cent). In 13 of the 26 cases of true recurrence (50 per cent), the stones formed in the first three years after operation. In 15 of these 26 cases, pyelolithotomy had been performed; in 5, nephrolithotomy, and in 6, ureterolithotomy. In 12 cases stones recurred only on the side on which operation was not performed.

Jasienski [4] reported an unusual case of renal stone of a type not hitherto mentioned in the literature. A man, aged 44 fell 4 meters (about 14 feet) a few years previous to observation; this was followed by crises of pain at various times, accompanied by hematuria. Roentgen examination disclosed multiple calculi extending into the subcapsular bed of each kidney. After several weeks, during which progressive anemia developed, right lumbotomy was done; the kidney was incised down its entire length, and the calculi were removed. One week later the patient's condition was so grave because of continuous hematuria and anemia that it seemed necessary to remove the right kidney, although the condition of the left kidney forbade it. The patient died the following day. At necropsy the left kidney was found to be small and full of stones but not otherwise diseased. In the right kidney, both the cortex and the medulla and also the calices contained a great number of irregular spaces varying from the size of a pinhead to that of a hazelnut, which were lined with crystalline concretions, in some places amorphous and in others exhibiting a granular structure. Histologic examination revealed that in the midst of very hard crystalline concretions were fibrinous masses and depigmented red corpuscles, encircled with concretions. Chemical analysis disclosed that these masses were composed almost half of albumin, probably fibrin, which was impregnated with calcium phosphate and contained some calcium oxalate. There was no evidence of any other constituents.

The anatomic lesions observed in the kidney probably explain the action of the concretions for a long time on the renal parenchyma. The inflammatory changes corresponded to the "lithiasic nephritis" of

4. Jasienski, George: Sur un cas rare de lithiase rénale bilatérale, J. d'urol. **34**:408 (Nov.) 1932.

Albarran. The numerous signs of cirrhosis and cicatricial changes, followed by great shrinkage in size, justified a diagnosis of cirrhotic lithiasis (Israel). The hematin composition revealed that the production of calculi was due to the renal hemorrhages. Around the clots were incrustations of urinary salts, following the course of the modified surface and constituting the mold for the stones. The absence of infection also showed that the calculi were due solely to hemorrhage. It is possible that there had been acute hemorrhagic nephritis.

Tumor.—Fischer [5] reported 48 cases of tumor of the kidney and of the renal pelvis. Thirty-five patients were operated on, and 6 refused to undergo operation. In 3 cases, exploratory incision showed that removal was impossible; in 2 of the remaining 4 cases, the general condition would not permit operation, and in the other 2, metastases to the bones and lungs were present. Histologic investigation revealed that typical or atypical hypernephroma was present in 29 cases. In 4 cases the condition was diagnosed as carcinoma, and in 4 others papilloma of the renal pelvis was present. In another case, that of a child aged 5 years, an adenosarcoma was present. The primary mortality in the cases in which operation was performed was 17 per cent; 3 patients died of myocardial weakness, 1 of shock resulting from the operation, 1 of pneumonia and 1 of uremia. In 13 of the 24 cases in which data were obtained there was local recurrence after the operation. Recurrence and metastasis occur most commonly in the first three years after operation. After that they are rare.

Harrah [6] stated that progressive enlargement of the abdomen of an infant or a young child should be looked on with grave suspicion. Malignant tumor of the kidney in infancy and childhood is not extremely rare. In many cases the enlargement of the abdomen is the only symptom for a long time. Absence of pain and hematuria, particularly the latter, early in the growth of the tumor is unfortunate from the standpoint of early diagnosis. The absence or late appearance of hematuria in cases of renal tumor of children may be connected with the growth capacity of the young kidney, which enables its structures to keep pace with the growth of the tumor and thus to preserve their continuity for a long time.

Harrah stated that the prognosis when these tumors are present is very serious. The best prospects, in his opinion, lie in a combination of radiotherapy and surgery. Because of the "silent" nature of the tumor in many cases, regional invasions and metastasis are likely to be present by the time the urologist or the surgeon first sees the patient.

5. Fischer, Karl: Ueber Neubildungen der Niere und des Nierenbeckens, Ztschr. f. urol. Chir. **37**:16 (April 22) 1933.
6. Harrah, F. W.: Embryonal Sarcoma of the Kidney in Children, J. Urol. **29**:445 (April) 1933.

Lipomatosis.—Young [7] described 11 cases of fatty invasion of the kidney, or replacement lipomatosis. In the first case, invasion occurred in the absence of infection, pyuria and nephrolithiasis. Although there was no evidence of infection within the kidney, there was slight evidence of perinephritis associated with the fatty invasion in all the cases. In all the cases there was an increase in the amount of perirenal fat, which was firmer than normal and surrounded the pelvis, entering the hilus around the vessels and the pelvis and following the infundibula into the kidney. The pelvis was always embedded in fat, and in some cases it was obliterated. The fat evidently invades the kidney, carrying fibrous tissue membrane before it, filling in preexisting spaces, invading the space between the cortex and the infundibula and calices and, when hydronephrosis is present, surrounding and compressing this until complete obliteration has occurred in some places. In 2 cases in which the condition was not associated with lithiasis, atrophy of the kidney had gone on to a remarkable degree.

Young stated that replacement lipomatosis is related to the process commonly known as autonephrectomy. Most extensive fatty invasion has occurred in completely obstructed kidneys. Atrophy of renal substance might be secondary to replacement by fat and the consequent cutting off of the blood supply. Replacement lipomatosis becomes important clinically, since this condition has been mistaken for a renal neoplasm. It may account for enlargement of the kidneys in cases of obstruction of the upper part of the urinary tract with or without the presence of stones. A different process in this condition, however, would lead to atrophy of a kidney and autonephrectomy.

Young stated the belief that true lipomas are rare; they are usually small and yellowish and are found as nodules encapsulated by fibrous tissue in the cortical layer distinctly beneath the kidney capsule. They result from rests of fatty tissue which have become included in the kidney during embryonic life. Replacement lipomatosis possesses none of these characteristics.

Krymholz [8] stated that atrophy of the kidney with substitution by fat, so-called lipomatosis perinephritis, is rarely observed. This should not be confused with a fatty tumor (lipoma) of the kidney or of its capsule. In the center of the fatty tissue. pus or a stone may frequently be found. The fatty substance of atrophic kidneys is not always firmly adherent around the stone; in some cases roughness of the stone or

7. Young, H. H.: Lipomatosis or Destructive Fat Replacement of the Renal Cortex. J. Urol. **29**:631 (June) 1933.

8. Krymholz, M.: Zur Fettsubstitution der atropischen Niere. Ztschr. i. urol. Chir. **36**:343 (March 11) 1933.

spurs are not found; that is, the stone is free in the substance. Fatty changes of the kidney as well as fatty substitution in the atrophic kidney may also be associated with tuberculosis.

Krymholz expressed the belief that renal atrophy and substitution by fat result from a disturbance of the blood supply of the organ; later inflammation of the solid substance of the kidney and hyperplasia result from irritation. The general process of replacement by fat is carried on by long drawn out, chronic infection of low degree.

Cysts.—Blum [9] reported a case of echinococcic cyst of the kidney in a man. Examination revealed one small cyst coming down from the ureter. The patient had passed cysts with the urine for a number of years. Nephrectomy was satisfactorily performed.

Blum stated that 40 per cent of the reported cases of this kind have occurred among workers who handled pigs and cattle. Another source of infection is pets that have access to slaughter-house material. Children become infected through contact with pets, and adults through contact with the children.

Tuberculosis.—Salleras [10] stated that although pyelography reveals nothing of value in the initial stages of renal tuberculosis, it is possible later to make a diagnosis by means of pyelography alone even in the absence of all other characteristic signs, such as the presence of the Koch bacillus, Colombino's sign, a decrease in the amount of urea and decisive cystoscopic signs. One need not wait to learn the results of inoculation of guinea-pigs. The pyelographic evidences of renal tuberculosis may be summarized as follows: The lesions begin in the renal papilla and advance progressively. This advance appears in the form of hollow pouches which increase in size with the age of the process, the same image, as well as the identical form, being repeated with equal clearness in all cases, thus making the picture characteristic. By this means Salleras was able to establish: (1) whether the condition is tuberculous pyonephrosis or some other form of pyonephrosis; (2) whether the disease is in the initial or in an advanced stage; (3) whether it is unilateral or bilateral and, if the latter, which kidney exhibits the greater destruction, and (4) whether there is transmission of the renal process to adjoining organs.

The differential diagnosis is based essentially on the fact that in nontuberculous pyonephrosis the dilatation begins in the ureter or pelvis and is then transmitted to the renal parenchyma, finally assuming the

9. Blum, Viktor: Ueber Nierenechinococcus, Ztschr. f. urol. Chir. **37**:46 (April 22) 1933.

10. Salleras, Juan: Valor de la radiografía simple en la localización de la tuberculosis renal y de la pielografía en el diagnostico de la misma, Bol. y trab. de la Soc. de cir. de Buenos Aires **16**:1216 (Oct. 26) 1932.

appearance of a single large cavity. In tuberculous pyonephrosis, on the contrary, both the ureter and the renal pelvis preserve their shape, the cavity at the level of the renal papilla beginning late and extending thence in an eccentric and shaggy form, by ulceration, to the cortex, as may be seen in the pictures included in the original article.

It is possible, accordingly, in a tuberculous kidney, to follow step by step the distinct phases of ulceration, from simple clouding of the outline of the corresponding calix to deep ulceration and even, in exceptional cases, to ulceration of an adjoining organ (intestine). In other words, pyelography serves to measure the anatomic value of the tuberculous kidney.

Tuberculosis of one or of both kidneys is then easy to recognize by the clear and regular outline of the papillary portion of a sound organ or by the eroded, shaggy and distorted appearance of the papilla and cortex if the kidney is diseased. The diagnosis of unilaterality or bilaterality of the papillary lesions can then be made, and in the latter case, it can be determined which side is more severely affected. The extent of injury to the kidney that has been partially destroyed by caseation can also be measured; bilateral pyelograms are an interesting guide in the decision for or against nephrectomy.

When the lesions have invaded the perirenal tissues or a nearby organ, the pyelographic images faithfully record such invasions by exhibiting shadows and distortions which, starting from the renal papilla, extend to the corresponding perirenal zone or establish communications with adjacent organs.

The use of excretory pyelography with iopax or skiodan, although satisfactory in some cases in which retrograde pyelography cannot be carried out, gives rather uncertain images, for although it produces fair shadows of cavernous lesions, the impossibility of basing a diagnosis on these is admitted. The relation between the elimination of opaque products and the quantity of renal parenchyma teaches that in the greater lesions there is less excretion than is needed to fill such ulcerations sufficiently to make them recognizable.

[COMPILERS' NOTE.—There is no doubt that it is possible by roentgenography alone to diagnose well advanced renal tuberculosis in which caseation of the organ is the predominant feature, as in certain cases of occluded renal tuberculosis or of closed tuberculous pyonephrosis which have been recorded in the literature as instances of autonephrectomy. Pyelography beyond question is one of the greatest advances for establishing a correct diagnosis of renal tuberculosis, as well as of any other lesion of the kidney. The indications for nephrectomy, however, should be based on the diminution of function of the organ with reference to elimination of urea or excretion of phenol-

sulphonphthalein, on the presence of the Koch bacillus in the catheterized specimen and on a positive pyelogram. This triad of clinical data is essential for reaching a definite diagnosis, since the presence of the bacilli of tuberculosis in the excreted urine does not always mean surgical renal tuberculosis.[11]

Rupture of a pyonephrotic tuberculous kidney, leading to a perinephritic abscess and then to a renocolic or a nephrobronchial fistula, although rare, has been recorded in the literature in several instances. Crenshaw[12] recently reported 2 cases of pyonephrosis with nephrobronchial fistula observed in a series of 256 cases of perinephritic abscess.

It is obvious that although intravenous pyelography, as Salleras stated, will not always solve the problem of the diagnosis of renal tuberculosis, it is of definite value in cases in which catheterization of the ureters cannot be accomplished and also in early lesions of the medullary or cortical renal substance, which have no connection with the excretory apparatus of the organ.]

Saenz and Eisendrath,[13] in the course of studies of the respective sensibility of methods of direct culture of the bacillus of tuberculosis, observed that performing "raclage" (harvesting or scraping together several cultures) of the tubes that had been sown with suspected material before any macroscopically visible culture appeared was of great advantage as a practical means of establishing an early diagnosis. They accordingly reported the results of a bacteriologic and clinical study of 57 cases in which renal tuberculosis was suspected. By a special technic they succeeded in isolating the bacillus of tuberculosis. In 30 specimens of urine the result was positive, and in 27 it was negative. Of the 30 cases in which the results were positive, 20 showed the bacilli on direct examination. After culturing, it was possible by means of "raclage" of the tubes to discover microcultures of acid-fast bacilli in the 30 positive cultures after eight to thirty days (in most instances within ten days), whereas the macrocultures did not appear until after from fifteen to sixty days. It was thus clear that a diagnosis could be made by their microculture method in half the time required for macroculture. It is worthy of note that in the 57 cases the results of direct examination, carried out simultaneously at the Pasteur

11. Gutierrez, Robert: Nonsurgical Renal Tuberculosis, Am. J. Surg. **5**:99, 1928; Diagnostic et traitement chirurgical de la tuberculose rénale, J. d'urol. **31**:126 (Feb.) 1931.

12. Crenshaw, J. L.: Pyonephrosis with Nephrobronchial Fistula, J. Urol. **28**:427 (Oct.) 1932.

13. Saenz, A., and Eisendrath, D.: La "microculture" et son importance dans le diagnostic précoce de la tuberculose rénale par l'ensemencement des urines, Presse méd. **40**:1856 (Dec. 10) 1932.

Institute and at the Necker Hospital, agreed in every respect. One interesting urologic discovery was the close relationship between the elimination of the bacilli of tuberculosis and the pathologic lesions of the patient. When the case is one of renal tuberculosis in which the focus is almost excluded, that is, when the renal pelvis is very small, bacilli of tuberculosis are found only intermittently. The study also revealed that bacilluria persists much longer after nephrectomy than has been supposed. In most cases, it disappears within the first six months following the operation, except when there is unsuspected bilateral infection. In 4 cases in which the patients were examined, two, four, five and six years, respectively, after nephrectomy, the culture was still positive. This shows that cultures should be made more often for the study of such postoperative signs as frequency of urination and cloudy urine.

From this study it becomes clear that it is unsafe to remain content with the result of direct culture alone, for this will be insufficient in 25 per cent of the cases. It is indispensable to culture the sediment of from 20 to 50 cc. of urine on from six to eight tubes of medium prepared according to the special technic described by Saenz and Eisendrath, and especially to examine systematically the product of "raclage" of every tube from the eighth day on. In this way an early precise diagnosis may be made in many cases in which direct examination of the sediment gives negative results. This method is more rapid and more reliable than inoculation of guinea-pigs. It has the advantage of permitting isolation of acid-fast bacilli (avian, paratuberculosis) that are nonpathogenic for the guinea-pig, and it also permits immediate identification of human or bovine types. The simplicity and ease of the method and the accuracy of the results make its use desirable in the future in the diagnosis of renal tuberculosis.

[COMPILERS' NOTE.—It is gratifying that a new routine procedure for the detection of the bacillus of tuberculosis has been established. The method described appears to be more accurate than inoculation of guinea-pigs, culturing on potato mediums and routine examination of smears, methods so commonly in use. It is also of interest that the Necker school [14] has again brought to light a well known phenomenon clearly described years ago by Albarran,[15] namely, the frequent finding of the bacilli of tuberculosis in the urine excreted by the sound kidney, even a long time after nephrectomy.]

14. Motz, Charles: Les pyonéphrites. Arch. urol. de la Clin. de Necker **7**:222 (Nov.) 1932.

15. Albarran, J.: Lésions du rein du coté opposé dans la tuberculose rénale unilatérale, Ann. d. mal. d. org. génito-urin. **26**:81, 1908.

Hydronephrosis.—Walters,[16] in a consideration of the conservative treatment of hydronephrosis, stated that if the renal parenchyma is functioning normally enough, removal of the obstructing factors which produce the hydronephrosis should give relief from the obstructive symptoms, and the pelvis and calices should return to within reasonably normal limits of size. In his experience, resection of the hydronephrotic renal pelvis gives excellent results in the treatment of hydronephrosis in properly selected cases. Ureteropyeloneostomy has relieved for almost four years hydronephrosis of a solitary kidney in which obstruction was complete at the time of operation.

Walters stated that if a surgeon chooses to reimplant the ureter into the dependent part of the renal pelvis, accurate anastomosis should be made between the cut end of the ureter and the opening in the pelvis, for any redundant portion of the ureter extending into the pelvis may serve as an obstructing valve. He stated that conservative procedures, such as resection of the renal pelvis, reimplantation of the ureter and removal of such obstructions as peripelvic tissue, are most strikingly indicated when the hydronephrosis is bilateral or when it is unilateral but sufficient renal parenchyma remains to justify the preservation of the organ. The necessity for the use of conservative procedures for the relief of obstruction when the kidney is solitary is apparent. In making the decision as to the best conservative procedure to follow, the guide is the surgeon's own experience, it being remembered that the safest and the best procedure is that which produces adequate and complete relief of the obstruction with minimal disturbance of the renal pelvis and the ureteral tissues.

Young[17] stated that the trend of surgery is more and more toward conservatism in the treatment of renal diseases, particularly hydronephrosis. It used to be thought that when a kidney was functionless or badly infected or had a greatly dilated pelvis nephrectomy was indicated. Physicians did not realize that by good drainage such kidneys can be brought back almost to a normal condition and the infection eradicated. Young recently observed a case in which there was a hydronephrotic sac which held about 4,000 cc. The fluid within it was thickly purulent, and there was no renal function, as revealed by the phenolsulphonphthalein test. The use of an indwelling ureteral catheter after a few weeks brought this apparently completely destroyed kidney back to equality with that on the opposite side. At operation, in which the obstruction was found to be due to a vascular cord, Young was able

16. Walters, Waltman: The Conservative Treatment of Hydronephrosis by Resections of the Renal Pelvis and Other Plastic Operations, J. Urol. 29:121 (Feb.) 1933.

17. Young, H. H.: Discussion of Kidney Surgery, J. Urol. 29:148 (Feb.) 1933.

by a new technic to remove the ureter from propinquity to the vascular cord by anterior and posterior plastic operations and to obtain a cure without either dividing the cord or transplanting the ureter. Since that time this technic has been carried out in several cases by Young and his associates with equally good results; the author feels certain that in cases of hydronephrosis produced by vascular cords compressing the ureter at its juncture with the pelvis, this operation will give good drainage of the pelvis and cure the hydronephrosis.

Rupture.—Ewell [18] stated that traumatic rupture of a hydronephrotic kidney, although rare, should be borne in mind if renal injury is suspected, as its presence may alter the operative treatment in a given case. Cases in which rupture of the kidney in children is suspected as a result of mild trauma are usually cases of hydronephrotic kidney. The symptoms are more variable in cases of rupture of hydronephrotic kidneys than in cases in which the kidneys are normal. Primary nephrectomy is the treatment of choice; however, in the light of knowledge of the surgical treatment of hydronephrosis, it may be possible in some cases to perform a conservative operation.

Aneurysm.—Gerard,[19] on the basis of 61 cases recorded in the literature as instances of aneurysm of the renal arteries (49 true and 12 false), repudiated the idea that any but true aneurysms exist, stating that the so-called false aneurysms are merely complications of renal contusions. The old classification of traumatic and spontaneous aneurysms must also be discarded as unsound. The symptomatologic triad of pain, hematuria and perirenal swelling, classically accepted, is accordingly false, being founded on a nonexistent basis, since it was found in only 5 cases (10 per cent). Aneurysms of the renal arteries are equally common in males and in females and in the right and in the left artery. They are almost always unilateral and solitary. They are almost always situated outside of the renal parenchyma and in the immediate vicinity of the hilus or internal to it, most often in intimate connection with the renal pelvis.

Nonruptured aneurysms develop in aged persons and are chiefly due to arteriosclerosis. They have a tendency to exhibit calcification. Clinically, they are manifested by pain in the region in which they are situated. When they are calcified, roentgen examination may reveal an "annular shadow," which is localized by pyelography at the hilus but outside the renal pelvis, thus making precise diagnosis possible.

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18. Ewell, G. N.: Traumatic Rupture of a Hydronephrotic Kidney, J. Urol. **29**:685 (June) 1933.

19. Gerard, Maurice: Les aneurysmes des artères rénales, J. d'urol. **34**:353 (Nov.) 1932.

Renal aneurysms that rupture develop as a result of the ordinary causes producing all aneurysms. They occur most often in young persons and produce no clinical manifestations, their course being insidious and their existence unsuspected up to the critical moment when they rupture. The prognosis in these cases is very grave. These aneurysms are a third more common than the nonruptured type. Rupture may be present in three clinical forms: 1. A pure hematuric form (33 per cent), with pain in the zone comprised. This type is difficult to diagnose by the common urologic methods; arteriography may be of assistance. 2. A form with perirenal tumefaction, which is more common (almost 50 per cent of cases). There are cataclysmic symptoms, a large perirenal collection of blood and a sensation of pain and pressure. Accurate diagnosis is almost impossible. The course is rapid, and the prognosis, grave. 3. A mixed form (rare), which is also very grave.

Treatment is always surgical. Gerard stated that treatment of nonruptured aneurysms has been attempted 5 times: in 4 cases of nephrectomy, and in 1 case by removal of the saccular aneurysm, with suture of the hiatus and conservation of the kidney. A cure was obtained in all the cases, but all occurred relatively recently. In the 29 known cases of ruptured aneurysm, 16 operations have been done: 3 between 1900 and 1906, and the others since 1914. In 4 cases the operations resulted fatally: Pinkert's case (laparotomy for occlusion by perirenal hematoma); Chisholm's case (exploratory laparotomy for perirenal hematoma); Janssen's case (exploratory lumbotomy followed by fulminating rupture of the aneurysm), and Hinman and Olson's case (nephrectomy). In the other 12 cases, in all of which nephrectomy was performed, the operations were followed by cure. Orth, in 1919, succeeded in removing the aneurysmal sac and in conserving a kidney with good function. This shows an interesting percentage (41.7) of cures attributable solely to operation.

In cases of calcified aneurysms, Gerard stated that good sense should dictate whether or not to operate, as in other conditions in aged or arteriosclerotic persons. In all cases of ruptured aneurysms, operation is imperative. With the pure hematuric form, there is plenty of time for all the necessary urologic examinations, but with perirenal hematoma and the mixed form, operation is practically always essential and delay cannot be risked. If it is in any way possible, however, the functional value of the two kidneys should first be determined. Lumbar nephrectomy is almost always the operation indicated for both ruptured and nonruptured forms. The pedicle should always be clamped promptly as a precaution against hemorrhage as a result of rupture of the aneurysmal sac during operation.

Decapsulation.—Putzu.[20] starting with the well known fact that the kidney is one of the organs regulating the acid-base equilibrium of the blood, undertook to see whether decapsulation caused any disturbance of this function. He made two series of experiments on dogs of medium size. In the first series, after testing the alkaline reserve of the blood, he decapsulated one kidney and then made tests twenty-four, forty-eight and seventy-two hours and five, eight, twelve, eighteen, twenty-five and thirty days after the operation. After a lapse of one month, he decapsulated the other kidney and performed the same tests before and after operation, at the same intervals. In the second series, he performed bilateral decapsulation in a single stage and made the same tests of the alkaline reserve and also tests of the renal secretory function.

In all cases the operation at first caused displacement of the equilibrium in an acid, never in, an alkaline, direction. This began after twenty-four hours and increased up to the fifth day; it then decreased from the eighth to the twelfth day, reaching the original level between the eighteenth and the twenty-fifth day. In 2 cases, in which the operative trauma was greater, the original level was not reached until the thirtieth day.

As a result of these experiments, Putzu concluded that decapsulation does not produce any important or permanent disturbance of the acid-base equilibrium, and that, therefore, from this point of view the operation is almost devoid of danger.

Resection.—Mastrosimone [21] studied experimentally the comparative results of simple resection and suture of the solitary kidney and of resection followed by the implantation on the resected surface of a fresh autoplastic graft composed of a section, 1 cm. thick, of renal tissue which had a moment before been continuous with that surface. His study was particularly concerned with hemostasis, with the final fate of the implant itself and with the nature of any changes in renal function that might occur. He found that renal resection followed by the use of an autoplastic graft secures complete hemostasis and is always available, whereas resection followed by simple suture is not without danger of hemorrhage (secondary and late) and is not always feasible, since the piece of renal substance removed must be wedge-shaped if one is to produce a breach that can be sutured. When the former method is used, intravascular thrombosis is produced on the cut surface of the kidney, a consolidation of the vessel content which

20. Putzu, F.: L'influenza della decapsulazione renale sulla riserva alcalina del sangue, Arch. ital. di urol. **10**:40 (Jan.) 1933.

21. Mastrosimone, C.: Resezione ed innesto autoplastico sul rene unico, Ann. ital. di chir. **11**:2226, 1932.

naturally affords it protection and also helps the graft to adapt itself. The tissues on both surfaces being the same, the capacity for coagulation develops more rapidly, and the hemorrhage that immediately follows resection disappears rapidly and completely instead of slowly and tediously as when simple suture is performed.

Although certain phenomena of necrobiosis and partial substitution of connective tissue occur in the graft, this process is so gradual that it does no harm. The renal function is maintained in equilibrium and reveals no changes sufficient to contraindicate the method. On the contrary, the presence of the graft appears to produce a greater and more rapid compensatory hypertrophy which stimulates better function in the part of the kidney that remains than is observed when the kidney is resected and repaired with simple suture.

Hypertrophy.—Calef [22] carried out studies on dogs for the purpose of discovering what histologic and functional modifications occur in the kidney remaining in situ after removal of the opposite kidney. He found that there are never any histologic lesions suggesting degeneration or proliferation of the parenchyma, but merely compensatory hypertrophy as a result of increased work and hyperplasia of the cells of the tubules and the glomeruli. Therefore, no increase in the number of renal elements was noted. The size of the glomeruli in particular was greatly increased for a certain time after operation, but it returned to normal later. The hyperplasia also seemed to present regressive phenomena after two weeks.

The compensatory hypertrophy in the dog is not permanent but lasts only until the renal elements are in a condition to exercise their entire function. When perfect function of the cells is attained and when their reserve energies enter into harmonious activity, the kidney regains both macroscopically (in weight and size) and histologically (in the appearance of the tubules and the glomeruli) the appearance that it had before operation.

In experimental animals the renal function may return to normal after four or five days. In a series of 13 human beings studied, seven or eight days were required if the removed kidney had been functioning well, but function returned almost at once if the removed kidney had been greatly changed. In man a period of polyuria follows the return of normal function, but this was never observed in animals. The author concluded that, regardless of whether or not the extirpated kidney has been functioning well or ill, the kidney left in situ is capable of carrying on the uropoietic function perfectly, histologic degenerative changes or excretion in the urine of pathologic substances never having been noted, either in human beings or in animals.

22. Calef, Carlo: Modificazioni istologiche e funzionali del rene superstite dopo nefrectomia unilaterale, Arch. ital. di urol. **9**:575 (Dec.) 1932.

Surgical Technic.—Beer [23] first presented his paper on the technic and indications for aseptic nephro-ureterectomy in 1921. He and his staff had performed 40 such operations without any operative mortality; this suggested that the added risk of removing the whole ureter through the second pararectus incision is negligible.

The technic of the operation has not been changed. The kidney is freed, and its vascular pedicle is carefully tied and cut across, leaving the kidney attached to the ureter. The ureter is then freed, the hand being insinuated retroperitoneally, with great care, well below the iliac vessels, which can always be recognized by the pulsation. If care is not exercised, it is conceivable that the peritoneum, particularly if unusually adherent, may be inadvertently torn. It is also necessary to adhere closely to the ureter, proceeding gradually as the periureteral adhesions are bluntly separated with the fingers. When the ureter has been separated well down into the pelvis in this manner, it is tied with a heavy silk traction ligature, which lies on the patient's abdomen, and the devascularized kidney is replaced in the wound and covered with packing gauze. The patient is then rolled partly on his back so as to expose the iliac fossa and the region for the incision and the exposure of the ureter. An extraperitoneal avascular pararectus incision through the sheath of the rectus muscle is used for the approach to the ureter. No muscles are cut. The rectus muscle is pulled mesially, and the retroperitoneal space is rapidly entered. By traction on the silk ligature attached to the ureter, this structure is easily identified, hooked up and freed from the bladder as well as upward, so as to liberate it in its entire course. The kidney can then be exposed, and by drawing on the silk traction ligature, the kidney and the attached ureter, ligated at its lower end and unopened, are readily lifted out of the lumbar wound. Both incisions are closed in layers, with as little rubber dam drainage as possible.

Beer stated that the indications for complete aseptic nephro-ureterectomy are not often encountered, as may be noted by the fact that he has performed only 40 such operations in more than twelve years in a rather active service for patients with renal diseases. The three main indications for this operation are as follows: (1) papillary growths of the renal pelvis or ureter (4 cases); (2) tuberculosis of the kidney with marked stricture at the lower end of the ureter, associated with a large, dilated, very thickened or thinned ureter (empyema) (24 cases), and (3) hydro-ureteronephrosis or pyo-ureteronephrosis caused by intrinsic or extrinsic stricture at the lower end of the ureter, by a firmly impacted stone or by a unilateral dilated ureteral orifice (2 cases).

23. Beer, Edwin: Further Experience with Aseptic Nephro-Ureterectomy, J. Urol. **29**:135 (Feb.) 1933.

Infection.—Kindall [24] reported a case of pyelitis cystica and ureteritis cystica diagnosed by urography and confirmed at operation; so far as can be determined by a study of the literature, this is the first case conclusively diagnosed. Cystoscopy was not of diagnostic value since the bladder was not involved. The ureters were dilated because of obstruction of their lumens by the cysts, mechanically causing back pressure or interference with the peristalsis of the ureter.

Kindall suggested a method of treatment: Large ureteral catheters passed to the renal pelvis and left in place for several days may cause mechanical rupture of many cysts, and the injection of a solution of silver nitrate when the catheters are removed, by its astringent action, may destroy other traumatized cysts.

URETER

Tumor.—Spampinato [25] reviewed 88 cases of primary tumor of the ureter from the literature and added a case of his own. These rare tumors appear to owe their origin to some form of mechanical irritation, which is not infrequently furnished by the presence of calculi. The calculi themselves may, however, be secondary, resulting from urinary stasis with decomposition of urine, such as occurs in cases of disease of the prostate gland, or forming around coagulations of blood. Persons of both sexes are equally affected. The age of greatest incidence is between 50 and 60, but cases have been observed among patients aged from 32 to 80. The tumors may be of connective tissue, of epithelial tissue or of a combination of the two. They may be benign or malignant. Opinions differ as to which of these classes predominates, some authors having observed more malignant growths and others more benign growths in the ureter. Papillary carcinomas are more common than nonpapillary ones. There is a tendency to believe that when papillomas of the ureter are multiple they should be regarded as malignant from the outset.

The effect of the tumor on the remainder of the ureter and on the kidney is to cause an obstacle to the outflow of urine, resulting in urinary stasis with consequent dilatation above the point of obstruction. The walls of the ureter become greatly thickened and may even resemble a loop of intestine. As a result of exaggeration of its length the ureter becomes tortuous and describes long spirals. The dilatation is greatest in tumors situated low in the ureters and in those of long duration. The content may be urine alone (hydro-ureter) or urine mixed with blood

24. Kindall, Lloyd: Pyelitis Cystica and Ureteritis Cystica, J. Urol. 29:645 (June) 1933.
25. Spampinato, Carmelo: Tumori primitivi dell'uretere, Arch. ital. di urol. 9:347 (Oct.) 1932.

(hemato-ureter), or it may become purulent as a result of secondary infection. The renal pelvis dilates and may become hydronephrotic. Metastasis follows either the lymphatic or the hematic route. Sometimes the retroperitoneal lymph nodes are infiltrated, with secondary carcinomatous development. Metastasis may also find its way to various organs of the body, and local diffusion may occur into the bladder, rectum, vagina, iliac bones or iliac vessels. The tumors vary in size from that of a walnut to that of a lemon, or they may even be much larger, especially if the growth is sarcomatous. They occur more often in the lower part of the ureter and more often in the right ureter than in the left.

The three principal symptoms are hematuria, pain and tumefaction. These are not pathognomonic, however, and there is no unanimity of opinion as to which predominates or as to the type of pain, which differs widely in individual cases. The differential diagnosis from renal tumor is very difficult because of the similarity of the symptoms. Cystoscopy is sometimes decisive, for example, when it reveals a neoplastic plug protruding constantly or intermittently into the bladder from a ureteral meatus. In 40 per cent of the cases the condition is diagnosed at operation or after death. Various erroneous diagnoses have been made, such as iliac sarcoma, ureteral calculus, vesical papilloma or tumor of the kidney. If the ureteral catheter meets an obstacle, calculus should first be thought of, but the obstruction may be a kink or a tumor. A rule that is more or less sound, but not absolute, is that if during a hemorrhage examination reveals an obstruction without the shadow of a calculus, and if the hemorrhage increases in the course of maneuvers, a tumor of the ureter should be suspected. If a tumor is present, the flow of urine will lack its customary rhythm; atony of the pelvis and ureter causes excretion of the urine drop by drop. If urohematonephrosis is found, it suggests a tumor of the ureter or pelvis. In some cases the catheter may remove a fragment of the tumor. If hematuria and pain persist after nephrectomy, it should be suspected that the ureter is at fault. Since this involves two operations, with loss of time and errors in prognosis, it is of great importance to make the correct diagnosis in advance of operation. When a tumor of the ureter has been diagnosed, the ideal procedure is nephro-ureterectomy in one or two stages. The performance of a more limited operation on the ureter alone in order to cause less trauma is not a sound practice in view of the fact that the renal function is often diminished when there is a tumor of the ureter (hydronephrosis, secondary infection, pyonephrosis), which demands removal of the kidney as well. In addition, there is the possibility that a tumor appearing in the ureter may in reality be secondary to a tumor of the kidney or of the pelvis.

.*Stone.*—Ravich [26] reported 758 cases of ureteral stones, 529 (69.8 per cent) of which occurred among males, and 229 (30.2 per cent) among females. There were 685 cases of single and 73 of multiple stones. Three hundred and forty-two patients had ureteral calculi on the right side, 404 on the left side and 12 on both sides. In 684 cases roentgenograms gave positive evidence of stones, and in 74 cases the results were negative. In 54 of the cases in which the results of roentgen examination were negative a scratch on the wax tip of the catheter indicated the presence of a stone. In 8 of the remaining 20 cases, stones were found projecting from the ureteral meatus; in 2 cases the diagnosis was arrived at from the appearance of the orifice; in 1 case a defect in filling was apparent in the urogram, and in 9 cases stones were found free in the bladder. At times the grating noted on withdrawal of the catheter assisted in making the diagnosis. In Ravich's practice the wax-tipped catheter was as important in making the diagnosis as were roentgenograms, and in the presence of stones composed of uric acid the use of the catheter was often the only measure whereby a diagnosis could be made.

Manipulative cystoscopic measures were necessary in most of the cases in this series. With these procedures Ravich included: the simple passage of a ureteral catheter to dislodge the stone; dilatation of the ureter by indwelling single or multiple catheters or by ureteral bougies; extraction by means of a stone dislodger of stones impacted within the ureteral orifice or the intramural portion of the ureter; enlargement of the ureteral orifice either by an electric cutting current or by scissors, and finally, lithotripsy of a growing vesical stone by his lithotriptoscope. In the remaining cases the stones either were passed spontaneously or required open operation. In 48 cases the calculus was passed spontaneously; in 456 it was passed after the simpler cystoscopic manipulations; in 37 it was extracted from the ureteral orifice, and in 20 it was found in the bladder and extracted.

Ravich stated that urinary stasis seems to be the only constant factor necessary for the formation of a stone in the urinary passages. The chemical character of the stone seems to depend on the hydrogen ion concentration of the urine, which may change from time to time and thus accounts for the different laminae so often demonstrated in stones. Calculi seem to form when as a result of urinary stagnation some change occurs in the secretory function of the tubular epithelium, causing coalescence or diminution of the protective colloids and consequent precipitation of the unattached crystalloids. Trauma, faulty diet, infection and foreign bodies are often contributory causative factors in the presence of stasis.

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26. Ravich, A.: Critical Study of Ureteral Calculi, J. Urol. **29**:171 (Feb.) 1933.

The fact that ureteral calculi occur twice as frequently among males as among females, and the 80 per cent incidence among adults aged from 21 to 50 correspond with the incidence of inflammatory conditions of the adnexa. This is borne out by the fact that in the 393 examinations of the prostate gland recorded, only 82 men (21 per cent) had what appeared to be normal prostate glands and seminal vesicles; the remainder revealed some degree of recognizable pathologic change. The passage of ureteral stones is hindered by physiologic narrowings, kinks, strictures, fixation of the ureter and atony of the ureteral musculature.

Spasm.—Samaan [27] made a comparative study of the action of the antispasmodic drugs papaverine, atropine and "visammin" on the intestine and the virgin uterus of the rabbit, on the ureter of the bull and of man and on the fundus of the dog's bladder. He found that these drugs do not influence the tissues to the same degree and under the same conditions of spasm.

Preparations of the tissues were stimulated by barium chloride, which acts directly on plain muscle tissue and contracts it, and by arecaline hydrobromide, which causes contraction by stimulation of the parasympathetic nerve endings in plain muscle tissue. In addition, "ammi visnaga" was used clinically on patients with impacted ureteral calculi.

It was found that atropine relaxes the intestine and the virgin uterus of the rabbit, the ureter of the bull and of man and the dog's bladder if they are made spasmodic through stimulation of the parasympathetic nerves; it fails to relax these organs if the cause of the spasm is directly muscular. For the bladder or the uterus, visammin and papaverine are of practically equal value in causing relaxation. Relaxation results when the spasm is mediated through the nerve, through the muscle or through both. Both papaverine and visammin relax plain muscle tissue by direct action. In the same concentrations papaverine is more effective than visammin on the intestine, whereas the contrary is true for the ureter of the bull and for that of man. This renders visammin superior to papaverine in the treatment of spasm of the ureter and of ureteral stone. Relaxation results when the spasm is mediated through the nerve, through the muscle or through both.

Clinical evidence of the therapeutic value of ammi visnaga in relaxing the ureter of man and thus allowing an impacted ureteral stone of suitable size to pass out through the natural passage or to descend to the bladder is presented.

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27. Samaan, Karam: The Pharmacological Basis of Drug Treatment of Spasm of the Ureter or Bladder and of Ureteral Stone, Brit. J. Urol. **5**:213 (Sept.) 1933.

BLADDER

Tumor.—Geisinger [28] stated that the entire group of nonepithelial tumors comprises only 10 per cent of all vesical neoplasms, and that when the adenomas, sarcomas, angiomas, lipomas and embryomas are excluded from consideration, the field obviously becomes very much narrowed. In all, perhaps 50 cases of fibrous or muscular tumors of the bladder have been reported in the literature.

In view of the fact that the muscular tumors of the bladder often do not produce symptoms and are discovered only at necropsy, it is probable that they occur more commonly than this statement indicates. Although they may occur in any situation, fibromas or myomas are generally found on the trigon or on the posterior wall of the bladder. They may be submucous, pushing into the vesical cavity, sometimes with a long pedicle; interstitial, corresponding to an intramural fibroid of the uterus, or peripheral, projecting into the perivesical tissues or the peritoneal cavity. Histologically, the pure fibromas may be hard and slightly vascular or soft and highly vascular. In either case they are composed essentially of interlacing bands of fibrous tissue. Smooth muscle cells may or may not be intermixed to a varying extent, and the blood vessels may be greatly dilated. The growths are usually sharply demarcated, and there is no true infiltration of the vesical wall. They are typically benign, but malignant degeneration may occur in rare instances. Calcification, fatty changes or necrosis may be present, especially in the hard fibromas on account of their poor blood supply.

There may be no symptoms. When the tumor is submucous it is more likely to give some indication of its presence at an earlier stage. although this type of growth also may exist for a long time without disturbing the patient. Involvement of the ureteral orifice will cause obstructive symptoms referable to the corresponding limb of the upper part of the urinary tract.

Geisinger concluded that the treatment should be surgical. Even if accidentally discovered, the tumors should be removed. Subsequent growth may produce marked symptoms, and though malignant degeneration is rare, there is a definite danger of its development.

Barringer [29] stated that hematuria is a diagnostic symptom of tumors of the genito-urinary tract. He expressed the belief. moreover. that after irradiation of, and presumably after operation on. vesical tumors, hematuria is an important symptom. He stated that in 75 per cent

28. Geisinger, J.: Fibroids of the Urinary Bladder, J. Urol. **29**:661 (June) 1933.

29. Barringer, B. S., in discussion on Rathbun. N. P: Hematuria. J. Ur. **30**:23 (July) 1933.

of his cases in which irradiation was carefully carried out and bleeding occurred afterward, hematuria indicated that he did not have control of the tumor, and the growth recurred.

Coffey [30] reported 11 cases of cystectomy for carcinoma of the bladder. There were 3 deaths as a result of the operation—a mortality rate of 27.27 per cent. In 2 cases in which the operation was performed in two stages on women (first, ureteral transplantation, and second, cystectomy), the patients were alive and well. Two women who had far advanced carcinoma of the bladder which had been treated on numerous occasions by irradiation and fulguration died as a result of an attempt to perform transplantation and cystectomy at one time. In 1 of these cases it was unwise to operate at all. The difficulties encountered in these 2 cases revealed special problems which indicate that the combined operation is unpractical for women even if the condition is favorable for operation. Cystectomy was performed on 7 men with transplantation of the ureters at the same operation. There was 1 death —a mortality rate of 14.28 per cent. Five men were alive and well, and all had been seen or heard from within a month of the presentation of Coffey's paper. All had been examined within five months. Therefore, Coffey stated that 7 were symptomatically cured without evidence of recurrence following cystectomy for carcinoma of the bladder. Aside from being perfectly well and comfortable, these patients were unusually happy and well satisfied with the results, as contrasted with patients afflicted with carcinoma of the rectum, who are often more or less morbid because of the inconvenience of a colonic stoma.

Coffey stated that these results compare favorably with the results of treatment of carcinoma in any other part of the body. In fact, this limited experience, together with the knowledge that as a rule carcinoma of the bladder remains a local process for a long time before it metastasizes, leads to the hope that carcinoma of the bladder may yet be the most curable of all carcinomas which invade the body and that, with added experience, the operation when performed at an early stage of the disease will be no more formidable than any of the other major operations for internal carcinoma.

Coffey concluded that cystectomy for carcinoma of the bladder is probably one of the most successful operations that has been introduced for the treatment of carcinoma, for the reason that diagnosis is made early in the course of the disease whereas metastasis is late, and that with added experience the mortality rate undoubtedly will be low and the percentage of cures high. An essential part of the operation is transplantation of the ureters into the large intestine. This, to be successful,

30. Coffey, R. C.: Cystectomy for Carcinoma of the Bladder, Am. J. Surg. **20**:254 (May) 1933.

must be performed by the submucous method of implantation. The author proposed three principles of technic for its performance. The first method may be eliminated immediately. The third method, because of its simplicity, may be favored by some surgeons for the early stages of carcinoma of the bladder, in which the element of time is not important. For the same reason, it may encourage the performance of a radical operation early in the disease, as is done for carcinoma in other parts of the body. The chief criticism is that two operations are required for transplantation of the ureters. The second method is ideal for use in conjunction with cystectomy for carcinoma of the bladder because the two ureters are transplanted in one operation. In men, cystectomy is performed at the same time that the ureters are transplanted, with little, if any, additional risk. The objection is that special skill in the performance of intraperitoneal operations is required.

　　Smith and Mintz [31] studied 150 cases of tumor of the bladder with regard to age, symptoms, type of tumor, treatment and end-results. They analyzed 37 cases at necropsy as to the type and grade of carcinoma, the presence and distribution of metastasis and the existence of other pathologic conditions.

　　The authors stated that the grade of malignancy of carcinoma of the bladder has no demonstrable relation to its tendency to metastasize. Squamous-cell carcinomas metastasize almost twice as frequently as papillary carcinomas. One important cause of the poor results of operations for carcinoma of the bladder is the long delay between the occurrence of the first symptom and the patient's entrance into the hospital. A comparison of the results of treatment by resection, by electrocoagulation and by implantation of radium showed that the lowest number of deaths in the hospital occurred among patients treated by electrocoagulation (26 per cent), the next lowest number among patients treated by resection (32 per cent) and the highest number among patients treated by implantation of radium (41 per cent). The end-results of these three methods are approximately the same. The authors expressed the belief that no one method is suitable for all types of carcinoma. The surgeon should be prepared to employ whichever method seems best suited to the individual case.

31. Smith, G. G., and Mintz, E. R.: Bladder Tumor, Am. J. Surg. 20:54 (April) 1933.

(To be Concluded)

LYMPHOSARCOMA IN BONE

LLOYD F. CRAVER, M.D.

NEW YORK

AND

MURRAY M. COPELAND, M.D

BALTIMORE

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In the earlier stages extension of lymphosarcoma may take place through the lymphatics, but in advanced cases many of the organs show apparently true metastatic growths which are satisfactorily explained only on the basis of invasion of the blood vessels.[1] Reports of cases from the literature illustrate a direct extension of the disease to bones as well as hematogenous metastases.[2] Reports of larger groups of patients yield little or no information as to the incidence of involvement of the bone in lymphosarcoma.[3]

CLINICAL STUDY

The records of the Memorial Hospital for the Treatment of Cancer and Allied Diseases made available for analysis one hundred and sixty-

1. Ewing, J.: Lymphosarcoma, Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 412.

2. (a) Paullin, J. E.: Internat. Clin. 4:192 (Dec.) 1931. (b) Pohle, E. A., and Ritchie, G.: Radiology 18:635, 1932. (c) Kienböck, R.: Wien. med. Wchnschr. 77:193 (Feb. 5) 1927. (d) Busser, F.: Bull. Assoc. franç. p. l'étude du cancer 17:651, 1928. (e) Marquio, L.: Rev. neurol. 37:74 (July) 1930. (f) Desjardins, A. U., and Ford, F. A.: J. A. M. A. 81:925 (Sept. 15) 1923. (g) Goormaghtigh: Acad. roy. de·méd. de Belgique 12:116 (Feb.) 1932. (h) Bregman, L., and Steinhaus, J.: Virchows Arch. f. path. Anat. 172:410, 1903. (i) Helly, K.: Lymphosarcoma, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, p. 1063. (j) Seecof, D. P.: Colorado Med. 26:201, 1929. (k) Joseph, B.: Arch. Clin. Cancer Research 3:93 (June) 1927. (l) Kundrat: Wien. klin. Wchnschr. 6:211, 1893. (m) Perier: Thèse de Paris, 1884, no. 33. (n) Wieland, E: Virchows Arch. f. path. Anat. 166:103, 1901. (o) Volpe, A., and Bloise, N.: Arch. de méd. d. enf. 30:73, 1927. (p) Schreiner, B. F., and Herger, C. C.: Radiology 5:399 (Nov.) 1925.

3. Baldridge, C. W., and Awe, C. D.: Arch. Int. Med. 45:161 (Feb.) 1930. Goormaghtigh.²ᵉ

TABLE 1.—Lymphosarcoma

Case	Age	Sex	Duration of Disease Prior to Change in Bones	Symptoms Related to Changes in Bones (Before and After Roentgenographic Evidence)	Involvement of Bones*	Demonstrable Involvement of Viscera and Nodes	Microscopic Examination	Treatment of Bones	Laboratory Observations	Duration of Life Subsequent to Changes in Bones
1	59	F	2 years, 6 months	Tingling, numbness in fingers of right hand 1 year and 11 months before; pain in right hip 7 months before	Skull (C and P); right upper part of humerus (C); right scapula (O); pelvis (O); femurs (O)	Left femoral triangle, above left Poupart's ligament, right groin; infiltration in left cheek	Reticulum cell lymphosarcoma	High voltage roentgen therapy 12/5/30 to 6/19/31	Progressive secondary anemia; eosinophilia present	Died after 8 months, 2 weeks
2	19	F	1 year	Pain in left arm and back 6 months before; symptoms of compression of the cord 6 months before	Skull (C); left humerus (C); dorsal vertebra 12 (P); lumbar vertebrae 4, 5 (C and P); pelvis (C and P); femurs (O); bilateral pathologic fracture; tibias (C and P); left fibula (C)	Left cervical nodes, supraclavicular fossa, left axilla, left inguinal nodes, sternal nodes	Reticulum cell lymphosarcoma	Radium emanation pack, small doses 1/5/32 to 1/8/32; high voltage roentgen treatments; erysipelas and prodigiosus toxins (Coley's); transfusions	Marked secondary anemia, improved by transfusions	Died after 2 months
3	51	F	2 years	Pain in lumbar region 2 years before	Lumbar vertebra 3 (P)	Right axilla, deformity of stomach, splenic enlargement, mediastinum	Reticulum cell lymphosarcoma	Roentgen therapy	Moderate progressive secondary anemia; eosinophilia present	Died after 1 year
4	40	M	9 months	Pain in right pubic bone 9 months before; swelling of right groin 9 months before	Right pubic bone (C)	Cervical nodes, right groin, liver enlarged, mediastinum	Lymphosarcoma	High voltage roentgen therapy 8/25/31 to 9/10/31; radium emanation pack, 7/24/31 to 8/2/31	Progressive secondary anemia, slightly improved following transfusions	Died after 2 months, 2 weeks
5	62	M	1 year, 9 months	Unsatisfactory data	Right third rib (C)	Left mastoid region, cervical, epitrochlear and inguinal nodes bilaterally	Reticulum cell lymphosarcoma	High voltage roentgen therapy	Moderate secondary anemia; eosinophilia present	Living after 1 year
6	52	M	1 year	Tumor of left mandible 1 year before; deafness 3 months before	Left mandible (C)	Mass extending above temporal region and downward to mandible, mediastinum	Reticulum cell lymphosarcoma	High voltage roentgen therapy	Blood normal	Not followed after 6 months, 3 weeks
7	50	M	8 months	Unsatisfactory data	Left femur (C); pathologic fracture	Right cervical nodes, right tonsil, mediastinum	Lymphosarcoma	High voltage roentgen therapy	Unsatisfactory data	Died after 20 days
8	9	F	5 weeks	Mass in left cheek 5 weeks before	Left malar bone (C)	Mass in left cheek, nodes in left submaxillary region	Lymphosarcoma	Radium emanation pack, 9/6/24 to 9/14/24	Red cell count normal; moderate leukocytosis	Died after 1 year, 1 month
9	54	M	1 year, 3 months	Pain in lumbar region 3 months before; pain in interscapular region 5 months before; pain posteriorly in shoulder, on right later; symptoms of compression of the cord 2 months later	Thoracic vertebrae 1, 2, 3 (P)	Left cervical nodes, tonsils, inguinal nodes bilaterally	Lymphosarcoma	High voltage roentgen therapy 8/29/27 to 5/23/28; radium emanation pack 6/14/28 to 7/2/28; Radium emanation pack 10/26/25; low voltage roentgen therapy 8/4/25 to 9/3/25	Unsatisfactory data	Died after 5 months

10	50	F	6 months	Pain in right mandible 6 months before; teeth removed at intervals before	Left cervical nodes, left axilla, left supraclavicular fossa, inguinal nodes bilaterally	Right mandible (C)	Lymphosarcoma	Radium emanation pack 2/23/24; 4/16/24 to 4/17/24	Moderate secondary anemia	Died after 2 months, 1 week
11	44	M	2 months, 3 weeks	Pain in lower part of back 2 months before; pain radiating down left leg 2 months before; rigidity of lower dorsal spine on admission	Axillae, right supraclavicular fossa, inguinal nodes bilaterally, mediastinum	Lumbar vertebra 4 (O)	Lymphosarcoma	High voltage roentgen therapy 4/22/30 to 10/21/30	Severe secondary anemia; moderate eosinophilia; albuminuria	Died after 7 months
12	29	M	3 months, 2 weeks	Pain in lower part of abdomen 3 months and 2 weeks before; symptoms of compression of the cord 2 weeks before	Mass in left hypochondrium, retroperitoneal nodes, mediastinal nodes, terminal ileum, diaphragmatic pericardium, parietal pleura, epidural tissues, splenic enlargement	Lumbar vertebra 2 (C); right femur (O)	Reticulum cell lymphosarcoma	High voltage roentgen therapy 6/21/29 to 6/24/29	Blood normal	Died after 3 weeks
13	24	M	6 months	Pain in left hip 3 months before	Tonsils, cervical, inguinal and axillary nodes bilaterally, submaxillary region bilaterally, swelling of left hip	Left femur (C); pathologic fracture	Reticulum cell lymphosarcoma	High voltage roentgen therapy 8/20/32 to 9/6/32; total irradiation 8/22/32 (40% S.E.D.†)	Moderate secondary anemia	Died after 6 weeks
14	11	M	6 months	Pain in left shoulder 6 months before; swelling of left scapula 6 months before	Swelling of supraspinous fossa, splenic enlargement, pelvic nodes, mesenteric nodes, jejunum, kidneys, stomach	Left scapula (P)	Lymphosarcoma	Radium emanation pack 5/1/32 to 6/10/32	Moderate secondary anemia	Died after 5 months
15	32	F	10 months	Pain in right thigh immediately before; pain about right side of head 3 months before	Generalized lymphadenopathy; spleen and liver enlarged; retroperitoneal mass felt	Femurs (C); skull (C)	Lymphosarcoma	High voltage roentgen therapy	Severe secondary anemia; differential count revealed preponderance of lymphocytes; moderate eosinophilia; moderate leukocytosis near end of disease	Died after 7 months
16	65	M	2 years, 8 months	Insufficient data	Cervical nodes bilaterally, supraclavicular fossa, axillae, spleen, liver, inguinal nodes	Pelvis (P); spine; upper end of femur (P)	Reticulum cell lymphosarcoma	High voltage and low voltage roentgen therapy	Persistent moderate leukocytosis with an increase in lymphocytes; moderate eosinophilia	Living after 1 year
17	39	M	8 months	Pain and limping 1 month before	Left supraclavicular fossa, right cervical nodes, retroperitoneal region, left inguinal and femoral area	Pelvis (C)	Reticulum cell lymphosarcoma	High voltage roentgen therapy	Blood normal	Living after 3 months

* O denotes osteoplastic; P, osteoplastic involvement.
† S.E.D. indicates skin erythema dose.

four cases in which the diagnosis of lymphosarcoma was established by biopsy or at autopsy. Seventeen patients (10.4 per cent) were found to have involvement of the bone. In every instance the changes were demonstrable prior to death.

While the duration of lymphosarcoma before and after the involvement of the bone is variable, the total duration of the disease is shorter than that usually seen in Hodgkin's granuloma. Most of the patients died before completion of the third year of the disease. In eight patients the clinical course prior to involvement of the bone gave no suggestion as to the rate of progress of the disease following osseous changes. Of eleven patients in whom change occurred in bones within one year after the onset of symptoms (table 1), eight died a few months later. Five patients had evidence of lymphosarcoma from one year and nine months to four years and nine months before involvement of bones occurred. In one patient (case 14) lesions developed in the bones before other evidences of lymphosarcoma were apparent. At autopsy the lymph nodes were found to be involved. Two patients living at the time of writing have skeletal invasion which has existed for a year. In the patients who died, demonstrable changes in bones were noted from twenty days to one year prior to death.

The age incidence does not vary from that found in the general group of patients with lymphosarcoma. Too few cases with osseous changes are available to estimate the greatest age incidence. The patients were mostly past the age of 20 years. The extremes of age were 9 and 65 years. The ratio of males to females was 1.6 : 1 and was not different from that found in the general group of patients with lymphosarcoma.

Pain was an early symptom of involvement of the bone in eleven cases. The patients complained either of dull aching or of sharp lancinating pain. It could be accounted for by pressure on the nerves or by destruction of the bone. The pain was not infrequently referred down the arm or leg. Girdle pain was occasionally recorded. In one patient tingling and numbness were present in the fingers of the right hand one year and eleven months before osseous changes were demonstrated. Involvement of the mandible simulated toothache. Pain in the lower part of the abdomen was a feature in one case. This was soon followed by symptoms of compression of the cord.

Abdominal symptoms were recorded in two other cases of this series prior to death. In one patient (case 3) roentgenograms revealed a deformity about the cardiac end of the stomach. In the other patient (case 12) an abdominal exploration showed marked involvement of the terminal portion of the ileum. In a third patient (case 1) the autopsy showed infiltration of the stomach by lymphosarcoma.

The interval between the beginning of pain and the occurrence of demonstrable osseous changes varied from three months to two years.

Signs and symptoms of compression of the cord were noted in three patients. In two instances they were observed before roentgenologic evidence of invasion of the bone was obtained (cases 2 and 12). In one patient (case 9) signs of compression of the cord occurred five months after the appearance of osseous changes in the first, second and third dorsal vertebrae. In this case pain in the interscapular region preceded the changes in the bone by ten months. Extensive herpes zoster was observed about the right shoulder girdle five months previously.

Rigidity of the spine was not infrequently associated with vertebral pains.

CONSTITUTIONAL RESPONSE TO THE DISEASE

The blood picture was usually that of secondary anemia. In a few instances in which single blood counts were done the observations on the blood were normal. In the majority of patients the white cell count was normal. Transfusions temporarily improved the blood picture. The white cell count varied from that of leukopenia to that of marked leukocytosis. A detailed analysis is complicated by the repeated effects of irradiation on the hematopoietic tissues. In cases 15 and 16 leukocytosis was observed with a preponderance of cells in the lymphocytic series suggesting the development of low grade lymphatic leukemia.[4] In these two patients the white cell count showed lymphocytes ranging from 24 to 57 per cent. In fourteen cases the differential count of the white blood cells showed polymorphonuclear neutrophils ranging from 38 to 92 per cent. Ten patients were found to have from 1 to 8 per cent eosinophils. A mild leukocytosis was often reduced to a normal level by irradiation.

The urine rarely showed albumin. One patient's urine (case 16) was examined for Bence-Jones bodies and found to be negative.

In general the patients had no prolonged cachectic periods; as a rule they were in relatively good condition until near the end of the disease.

INVOLVEMENT OF THE BONE

A compilation of isolated reports of cases from the literature [2] indicates that the skull, spine and femur are most frequently involved.

In our material the bones involved were in the order of frequency: the spine, pelvis, skull, femur, humerus, tibia, scapula, mandible, fibula and ribs (table 2 and fig. 1). Pathologic fracture occurred five times. In case 2 pathologic fracture occurred in the left humerus and in both femurs.

Collapse of the diseased vertebrae was not commonly observed.

Roentgenographic Studies—Seen roentgenographically the lesions in the bones were either predominantly osteoplastic (fig. 2) or osteolytic

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4. Marquio.[20] Helly.[21]

(fig. 3). In the long bones the disease had no predilection for the part containing marrow but infiltrated the bones extensively (fig. 4). As the disease progressed, the entire bone was frequently involved. A progression of the disease was found to accentuate further the two

TABLE 2.—*Involvement of Bone in Sixteen Cases of Lymphosarcoma*

	Number of Cases	Number of Times	Right	Left
Vertebrae				
Thoracic 1	2	2	..	..
2	2	2	..	..
3	2	2	..	..
4	1	1	..	..
5	1	1	..	..
6	1	1	..	..
7	1	1	..	..
8	1	1	..	..
9	1	1	..	..
10	1	1	..	..
11	1	1	..	..
12	2	2	..	..
Lumbar 2	1	1	..	..
3	1	1	..	..
4	2	2	..	..
5	1	1	..	..
Pelvis				
Ilium	3	5	2	3
Pubis	2	3	2	1
Sacro-iliac joint	2	2	..	2
Sacrum	3	3	..	..
Ischium	..	1	1	1
Skull				
Frontal bone	2	2	..	..
Parietal bone	2	4	2	2
Malar bone	1	1	..	1
Femur				
Upper third	3	3	..	3
Lower third	1	1	1	..
Diffuse	1	1	1	..
Humerus				
Upper third	1	1	1	..
Diffuse	1	1	..	1
Tibia				
Upper third	1	1	1	..
Middle third	1	1	..	1
Scapula	2	2	1	1
Mandible	2	2	1	1
Fibula, upper third	1	1	..	1
Ribs, third	1	1	1	..

varieties of osseous change. In general, the osteolytic changes were seen more frequently.

Roentgenograms of the skull showed a predominant osteoclastic reaction (fig. 5). Small miliary or larger single punched-out areas of destruction were seen. The areas of destruction were rarely surrounded by increased bone density representing the formation of new bone.

A lesion in a rib (case 5) showed rarefaction without marked alteration in the structure of the bone.

The vertebrae showed sclerosis with some destruction of bone, occasionally with partial collapse (fig. 2). In two instances (cases 11 and 12) resorptive features predominated in the bones. A periosteal reaction about the diseased vertebrae was not seen.
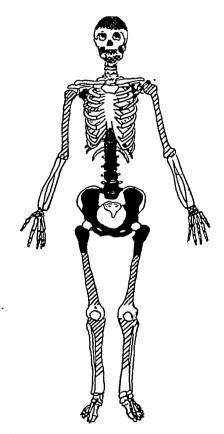
Fig. 1.—The solid black areas represent the sites most frequently involved; the checkered areas, the sites commonly involved; the diagonal lines, those invaded occasionally; the white portions, those rarely involved.

The pelvis, especially the ileum, was frequently involved. In case 2 (fig. 6) marked rarefaction with many small punched-out areas was observed in the ilium. The sacrum and fifth lumbar vertebra showed similar changes. In one instance (case 4) the pubis showed marked destruction with trabeculae not unlike a giant cell tumor (fig. 7). An osteolytic process predominated in all the pelvic lesions. The acetabula were involved less frequently than expected.

In the long bones a diffuse destructive process was common. Infiltration was the rule, often causing partial collapse of the diseased bone with fracture (fig. 4). Occasionally there was thickening of the cortex associated with a periosteal reaction (fig. 8). In some instances the destruction appeared centrally, eroding the cortex from within the
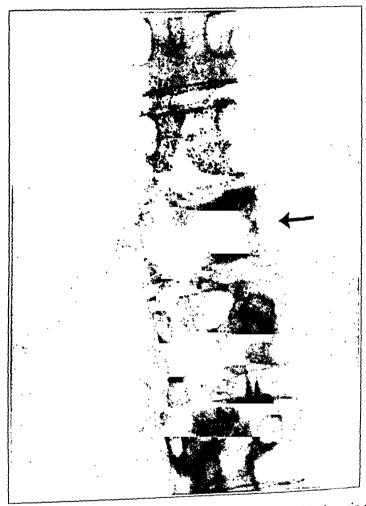
Fig. 2.—Roentgenogram depicting involvement of the twelfth thoracic vertebra. Note the predominant osteoplastic reaction. Areas of rarefaction are seen surrounded by bone of increased density.

marrow cavity. This reaction is seen in multiple myeloma and in metastatic carcinoma. The diffuse involvement of the bones with predominant osteolytic changes is characteristic of the disease. An osteoplastic reaction was noted principally in the vertebrae.

GROSS MATERIAL AND MICROSCOPIC STUDIES

A biopsy was done on every patient while under observation. A diseased gland was removed in each case. Autopsies were performed on three patients (cases 1, 12 and 14).

In case 12 the diseased femur was obtained at autopsy. The lower end of the bone was found encased in a mass of tumor which was
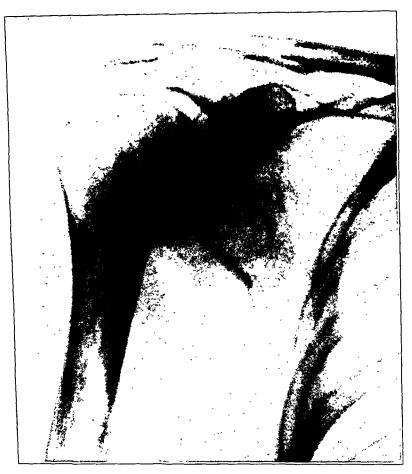
Fig. 3.—Roentgenogram of the scapula showing rarefaction and frank destruction along the axillary border. There is no periosteal reaction.

attached to and involved the periosteum, forming a cuff 5 cm. long and 1.5 cm. thick. The bony cortex was eroded by the tumor (fig. 9). The microscopic study (fig. 10) showed destruction of the bone by the tumor with no evidence of the formation of new bone. The tumor infiltrated through the haversian canals and extended beneath the periosteum. A mass of nodes was also found closely attached to the bone in the region of the fifth lumbar vertebra and in roentgenographic

studies this proved to be involved. This invasion of the bone was by direct extension.

In case 14 the left scapula was removed at autopsy. The supra-scapular fossa was found filled with a glistening rubbery opaque tumor
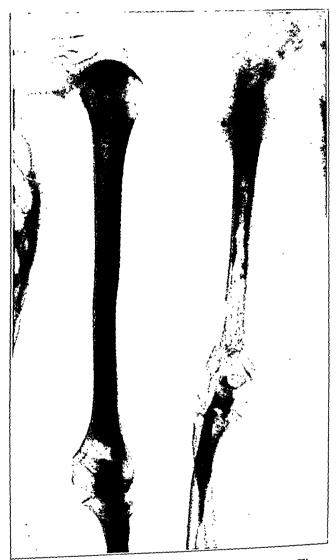
Fig. 4.—Note the diffuse involvement of the humerus. There is marked destruction with little or no formation of new bone. A pathologic fracture is seen at the upper end of the shaft. A slight periosteal reaction is seen about this area. The other humerus is normal.

mass about 4 mm. thick, extending from the acromion process across the supraclavicular fossa to the vertebral border and infiltrating the underlying bone. In both cases little or no periosteal reaction was present. Visceral lesions were found in all the cases examined at necropsy.
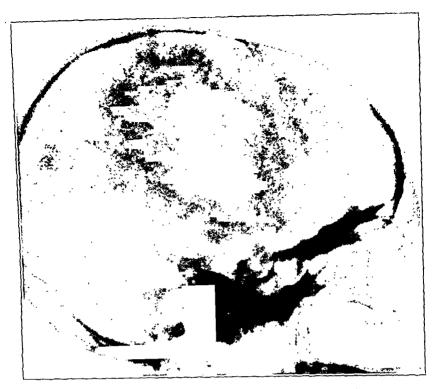
Fig. 5.—Roentgen ray picture of the skull showing small multiple punched-out areas of destruction. The areas of destruction were rarely surrounded by bone of increased density.

Fig. 6.—The pelvis shows marked rarefaction, especially in the left ilium, with many small punched-out areas. The sacrum and fifth lumbar vertebra show similar changes. The heads of the femurs are infiltrated and show marked destruction. Note the bilateral fracture of the femurs.

Of importance is the fact that when the tumor lies in close proximity to the bones direct extension of the disease to the bone occurs. The vertebrae are especially subject to involvement by direct extension.

Fig. 7.—Roentgenogram of the pelvis showing extensive involvement of the pubis. The trabeculations give a picture similar to that of giant cell tumor.

The microscopic appearance of the lymph nodes removed for biopsy was characteristic of reticulum cell lymphosarcoma: a diffuse growth of lymphoid cells lying in the reticular tissue. The general structure of the nodes was obliterated. The individual cells varied in size. Multinucleated cells were not observed (fig. 10).

DIFFERENTIAL DIAGNOSIS

Lymphosarcoma affecting bones may be confused with metastatic deposits in bones from carcinoma, Hodgkin's granuloma, Ewing's tumor, the leukemias and osteomyelitis.
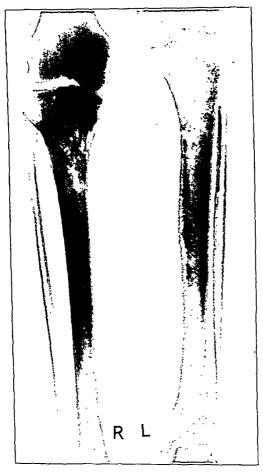
Fig. 8.—Roentgenogram of the tibias. The left tibia shows thickening of the cortex with some periosteal proliferation. Within the thickened cortex and in the upper shaft punctate areas of destruction are seen. An area of rarefaction and destruction is seen in the upper shaft of the right tibia. A periosteal reaction is visible on the lateral side of the shaft.

Varying degrees of enlargement of the lymph nodes with or without the presence of a splenic tumor are characteristic of the disease. A biopsy is of great value in establishing the diagnosis.

Metastatic carcinoma usually shows central destruction of the bone without a periosteal reaction. If seen in the earlier stages, the first

metastatic deposits are found near the point where the vessels emerge from the bone. As in Hodgkin's disease of the vertebrae and metastatic foci from carcinoma of the breast and prostate, lymphosarcoma may stimulate an osteoplastic reaction.

The leukemias may be differentiated from lymphosarcoma by studies of the blood. However, in the terminal phases of lymphosarcoma a lymphoid leukemia may develop, complicating the clinical picture, and

Fig. 9.—Photograph of bisected portion of the lower end of the femur. The lower end of the femur is encased in a mass of tumor which involves the periosteum. The cortex is infiltrated by the tumor, which also involves the marrow cavity.

there are cases of generalized lymphadenopathy in which the biopsy shows lymphosarcoma, but in which there is a low grade lymphemia and the course is similar to that of chronic lymphatic leukemia.

Hodgkin's granuloma is typified by a varying degree of involvement of the lymph node, with enlargement of the spleen, itching and secondary anemia. The changes in bones are much like those occurring in lymphosarcoma, and a biopsy of a lymph node is important for

the differential diagnosis. In osteomyelitis, especially in the early stages, destruction of the bone with a periosteal reaction may be mistaken for lymphosarcoma. The leukocyte count is of value. A sequestrum with a shaggy periosteal reaction characterizes the later stages of osteomyelitis. Atypical osteomyelitis, however, frequently requires a biopsy to establish its identity.

TREATMENT

As in Hodgkin's disease, one's main reliance in the treatment of lymphosarcoma is on irradiation. The gross lesions of the bone may

Fig. 10.—Microphotograph of reticulum cell lymphosarcoma involving the bone. The bone shows infiltration by the tumor. There is no evidence of osseous regeneration.

be treated either by single large suberythema doses or by fractional doses, with high voltage roentgen rays. Relief from pain is usually prompt. Reparative changes in the bones may be observed after treatment. In the terminal stages of the disease routine irradiation of all the bones is not attempted. This conservative attitude is taken because the severe anemia which exists in many of the late cases would only be aggravated by irradiation.

SUMMARY

1. One hundred and sixty-four patients with lymphosarcoma have been studied.

2. Seventeen patients (10.4 per cent) were found to have involvement of the bone.

3. The bones most frequently involved were those of the spine and pelvis.

4. Pathologic fracture was observed five times.

5. Collapse of the vertebrae was relatively rare. Signs of compression of the cord were noted in three patients.

6. Two types of osseous changes were noted: an osteolytic and an osteoplastic change. Osteolytic changes predominated. A combination of both was seen occasionally.

7. Two routes of involvement of the bone were observed: (1) the hematogenous route and (2) direct infiltration from contiguous diseased lymph nodes.

8. The histopathologic studies showed all the specimens to be reticulum cell lymphosarcomas.

9. The stomach was involved by lymphosarcoma in two cases; the ileum, in one case.

10. All the patients except one had evidence of involvement of the lymph nodes prior to demonstrable osseous changes.

11. In two patients a low grade lymphatic leukemia developed prior to death. Histologically the lymph nodes showed typical lymphosarcoma.

EFFECTS OF DIVERTING THE GASTRIC CONTENTS TO THE LOWER INTESTINAL LEVELS

PAUL E. McMASTER, M.D.

LOS ANGELES

As a result of much clinical and experimental work, the ulcer-producing effect of the gastric contents on the jejunal mucosa following gastrojejunostomy is well established. Few reports have been published concerning the effects of diverting the gastric contents to lower intestinal levels. This work was designed to study the results of shifting the outlet of the stomach to progressively lower levels from the duodenum to the colon, inclusive.

Rienhoff,[1] commenting on the incidence of jejunal ulcer after gastrojejunostomy, mentioned that it has occurred in as high as 25 per cent of clinical cases. He failed to find marginal ulcers following gastroduodenostomy, and having noted further that spontaneous ulceration of the third or inferior portion of the duodenum does not occur, advocated infrapapillary gastroduodenostomy in preference to gastrojejunostomy, although it is technically more difficult. After a series of experimental results in dogs, Ivy and Fauley [2] came to the conclusion that the duodenal mucosa is less sensitive to the acid gastric content than is the jejunal mucosa. They stated that if gastro-enterostomy must be done, pyloroplasty or gastroduodenostomy is preferable to gastrojejunostomy as far as postoperative ulcer is concerned. These investigators sectioned the duodenum about 1 inch (2.5 cm.) below the pyloric sphincter, then anastomosed the jejunum to the duodenum and drained the alkaline juices into the lower 15 inches (38.1 cm.) of the ileum. The acid gastric content thus came in contact with the upper duodenal and the jejunal mucosa. Of twelve dogs, eight died of perforating or bleeding jejunal ulcers. There were no duodenal ulcers.

An experimental comparison of the incidence of postoperative ulcer following gastro-enterostomy and gastro-enterostomy with duodenal drainage was made by Exalto [3] in 1911. In this study he performed gastrojejunostomy and failed to obtain jejunal ulceration in seven

dogs. In four dogs he performed a Y-anastomosis of Roux and encountered jejunal ulcers in three experiments. Following this he performed a gastrojejunostomy and then short-circuited the duodenal contents into the colon. He observed ulceration of the jejunum in each case. Leriche[4] stated that he had an occurrence of 6 per cent of jejunal ulcers after simple gastrojejunostomy, while after the Y-anastomosis of Roux the incidence was 16 per cent. Numerous investigators, such as Mann and Williamson,[5] Ivy and Fauley,[2] Matthews and Dragstedt,[6] Gallagher and Palmer[7] and Steinberg and Proffitt,[8] confirmed this high incidence of jejunal ulceration after short-circuiting the duodenal juices to the lower intestine, invaginating the upper cut end of the duodenum and performing either end-to-end or end-to-side anastomosis of the pyloric end of the stomach to the jejunum. Hence it is seen that the alkaline duodenal juices are important in the prevention of ulcer because of their neutralization of the acid gastric contents.

A marked decrease in resistance to the formation of peptic ulcer following ligation of the common bile duct was noted by Bollman and Mann.[9] In sixty-four dogs in which the common bile duct had been ligated, forty-one developed acute, subacute or chronic duodenal or gastric ulcers in from five to two hundred and ninety-five days postoperatively. Elman and Hartmann[10] drained the pancreatic juice to the outside by intubation of the pancreatic ducts in six dogs. The animals were kept in good condition by careful feeding and intraperitoneal reinjections of a "combined solution"[11] in 5 per cent dextrose. Spontaneous duodenal ulcers developed in each case. This work also illustrates the rôle of both bile and pancreatic juice in the prevention of peptic ulcer. The mechanism of this protection is probably through the neutralization of the gastric acidity by reflux into the

4. Leriche, R.: Pathogénie de l'ulcère peptique post-opératoire, J. de chir. **38**:465, 1931.

5. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

6. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer: Experimental Studies, Surg., Gynec. & Obst. **55**:265, 1932.

7. Gallagher, W. J., and Palmer, W. L.: Experimental Jejunal Ulcer: Relative Importance of Mechanical and Chemical Factors, Proc. Soc. Exper. Biol. & Med. **30**:468, 1933.

8. Steinberg, M. E., and Proffitt, J. C.: The Etiology of Postoperative Peptic Ulcers, Arch. Surg. **25**:819 (Nov.) 1932.

9. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

10. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

11. Hartmann, A. F., and Elman, R.: The Effects of Loss of Gastric and Pancreatic Secretions and the Methods for Restoration of Normal Conditions in the Body, J. Exper. Med. **50**:387, 1929.

stomach. The neutralizing power of duodenal juices is further shown by a comparison of the work of Dragstedt and Vaughn [12] and Matthews and Dragstedt.[6] The former workers, in order to study the resistance of the intestinal mucosa to gastric digestion, made a large window in the anterior wall of the stomach. The opening was then filled with an intestinal flap taken from various levels of the bowel. The flap was prepared as follows: A segment of intestine was excised, the blood supply to it being left intact, and the continuity of the intestines was reestablished by an end-to-end anastomosis. The isolated segment was opened by an incision along its antimesenteric border and sutured into the window cut in the stomach. In this manner the mucosa of the duodenum, jejunum, ileum and colon was exposed to the gastric contents. When the segments were examined twelve months later, the mucosa of each was entirely normal macroscopically and microscopically. Matthews and Dragstedt carried out a similar procedure with a segment of colon, but in addition inserted a one-way valve in the pylorus, which, because it prevented regurgitation of the duodenal juices into the stomach, produced ulceration of the mucosa of the colon.

That the chemical action of gastric juice will produce chronic ulcer is shown by the not infrequent clinical finding of a chronic or perforated ileac ulcer at the margin of a Meckel's diverticulum containing gastric mucosa as reported by Aschner and Karelitz [13] and Lindau and Wulff.[14] With the constant finding of typical gastric glands in these diverticula it is assumed that the acid secretion from the glands is the causative factor of the ileac ulcer. By anastomosing Pavlov pouches to a spur of the ileum, Matthews and Dragstedt [6] produced experimentally in dogs ulcers similar to those found in man adjacent to Meckel's diverticulum. Chronic progressive ulcers resulted in 100 per cent of the experiments. When Pavlov pouches were anastomosed to a spur of jejunum, ulceration occurred in 85 per cent of the animals.

In 1932, Rivers and Wilbur [15] found the reports of three cases of gastro-ileostomy and added reports of seven cases from the records of the Mayo Clinic. In the three cases from the literature which they reviewed as well as in their own cases, the anastomoses had been performed by mistake, and subsequent operation was necessary for the relief of persistent or newly acquired symptoms. Of the three cases

12. Dragstedt, L. R., and Vaughn, A. M.: Gastric Ulcer Studies; The Resistance of Various Tissues to Gastric Digestion, Arch. Surg. **8**:791 (May) 1924.

13. Aschner, P. W., and Karelitz, S.: Peptic Ulcer of Meckel's Diverticulum and Ileum, Ann. Surg. **91**:573, 1930.

14. Lindau, Arvid, and Wulff, H.: The Peptic Genesis of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **53**:621, 1931.

15. Rivers, A. B., and Wilbur, D. L.: The Syndromes of Gastro-Ileostomy and Gastro-Iliac Ulcer, Surg., Gynec. & Obst. **54**:937, 1932.

cited one showed a large, indurated gastro-ileac ulcer. Of their own seven cases gastro-ileac ulcer was found in two cases and gastro-ileitis in one. In all of the cases except one there was marked diarrhea, in some as high as from ten to twelve stools daily. Loss of weight was also a noticeable symptom.

EXPERIMENTAL WORK

The effect on intestinal mucosa, blood chlorides and body weight of dogs after the gastric content had been diverted to different levels in the intestinal tract was studied. After the stomach had been cut
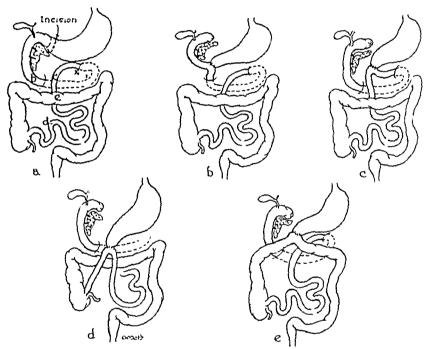
Fig. 1.—Diagrammatic illustrations showing, in *a*, the line of incision through the prepyloric portion of the stomach, and in *b*, *c*, *d* and *e*, the anastomosis of the open end of the stomach to the side of the duodenum, jejunum, ileum and colon, respectively.

through about 1 cm. proximal to the pyloric sphincter, the duodenal stump was invaginated, and the gastric end anastomosed to the side of the bowel at various levels from the duodenum to the colon, inclusive, as shown in figure 1.

Healthy adult dogs were used. Preoperative weights and estimations of the blood chlorides were recorded. Chlorides were determined as milligrams of sodium chloride per hundred cubic centimeters of blood. according to the method of Hawk and Bergeim.[16] Morphine-ether

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16. Hawk, P. B., and Bergeim, Olaf: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1927, p. 402.

anesthesia and the usual aseptic operative technic were employed. Clamps were used only on the stomach. In approximately half of the series catgut was used, while in the other half of the experiments linen was used for suture material. In none of the cases in which linen was used was there evidence of ulceration about the material when it was examined post mortem. The ulceration which occurred was separated by a zone of mucosa from the anastomotic line; hence in this series, the material of the nonabsorbable suture had no relation to ulceration. The animals received nothing by mouth for three days postoperatively, but they were given intravenous injections of a physiologic solution of sodium chloride daily. After this, they were fed the regular stock diet of ground meat and bread, and allowed to drink fluids. Daily observations were made for vomiting or diarrhea. Weights and determinations of the blood chlorides were recorded at irregular intervals but usually once a week, unless the animal was rapidly losing weight, when more frequent observations were made.

Thirty-five experiments were performed as follows: gastroduodenostomy, four; gastrojejunostomy, eleven (the sites ranged from a few centimeters to about 60 cm. distal to the duodenojejunal junction); gastro-ileostomy, ten (including levels from high in the ileum to within 15 cm. of the ileocecal valve), and gastrocolostomy, ten (the sites included the cecum and the ascending and transverse colon).

GASTRODUODENOSTOMY

The four dogs that underwent gastroduodenostomy lost no weight; two gained weight. They all maintained the preoperative blood chloride levels, and none acquired ulceration of the duodenal mucosa when killed and examined five, seven, ten and twelve months, respectively, after the operation. Linen had been used for the suture material in three of these dogs. The anastomoses were made at levels of from 10 to 16 cm. distal to the pyloric sphincter.

GASTROJEJUNOSTOMY

Of the eleven gastrojejunostomies performed, five produced jejunal ulcers, one of which was healed and four of which were chronic or perforated (figs. 2 and 3). Most of the animals maintained their preoperative weights unless symptoms of ulcer, namely, anorexia, vomiting, listlessness and tarry stools, developed, in which event there was usually a rapid loss in weight. Blood chlorides remained essentially the same as before operation, with a few unimportant variations in some of the dogs. Table 1 gives the results for this series.
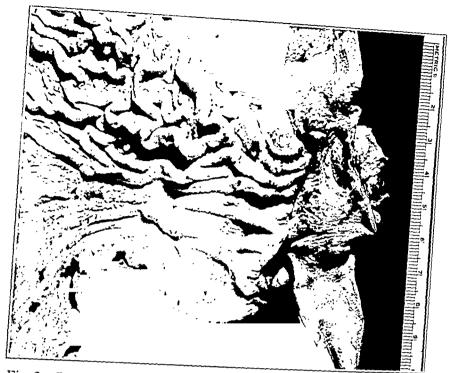
Fig. 2.—Perforated jejunal ulcer one hundred and eighty-eight days after gastro-jejunostomy. The ulcer is opposite the lower part of the anastomotic stoma.
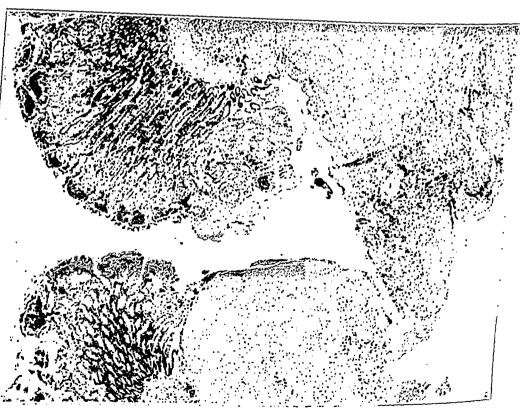
Fig. 3.—Photomicrograph of a perforated jejunal ulcer ninety-one days subse-quent to gastrojejunostomy.

GASTRO-ILEOSTOMY

Seven of the ten gastro-ileostomies led to definite discrete ileac ulcers (figs. 4 and 5). One animal revealed marked, diffuse ileitis extending distally for approximately 10 cm. from the anastomosis when examined at autopsy thirty-eight days after operation. It was also noted at postmortem examination that if the anastomosis was in the lower portion of the ileum, hemorrhagic colitis was present. This was seen grossly as superficial hemorrhages and small erosions in the mucosa of the large bowel. The irritation occurred practically always in the distal half of the colon, whereas the proximal portion of the large intestine was usually free from visible signs of irritation. Microscopic

TABLE 1.—*Gastrojejunostomy*

Dog	Duration of Experiment, Days	Cause of Death	Ulcer, Jejunal	Blood Chlorides		Weight, Kg.	
				Pre-operative	Just Before Death	Pre-operative	At Death
228	307	Peritonitis; perforated jejunal ulcer	+	390	410	19.1	10.2
220	339	Killed	0	402	442	15.8	14.8
217	146	Peritonitis; 3 perforated jejunal ulcers	+	424	408	13.5	7.8
218	125	Killed	0	442	484	12.2	11.4
222	8	Distemper	0	450	436	8.4	8.0
899	54	Distemper	0	462	446	15.0	13.8
460	94	Killed	0	...	...	15.4	14.0
924	104	?; very cachetic	+ healed	442	404	11.5	5.4
493	91	Peritonitis; perforated jejunal ulcer	+	452	448	17.3	16.0
649	97	Killed	+	476	506	9.8	9.4
219	188	Peritonitis; perforated jejunal ulcer	+	450	435	12.1	6.0

sections revealed multiple hemorrhages and small erosions in the mucosa of the distal half of the colon. If the anastomosis was in the lower portion of the ileum, the animals lost considerable weight and had bloody diarrhea; the blood chloride level fell in one case to 68 per cent of the normal value. When symptoms of anorexia, vomiting, bloody diarrhea and loss of weight appeared, a diagnosis of ulcer was made and in each case verified at autopsy. Table 2 gives the results of these experiments.

GASTROCOLOSTOMY

Ten animals were used, and the anastomoses were made into the cecum or into the ascending or transverse colon. The dog in this series which survived longest lived only twenty days. The most noticeable symptom was very severe and profusely bloody diarrhea. The animals rapidly became emaciated, although a few ate well. Some refused food and water. A secondary anemia with hemoglobinometer readings of
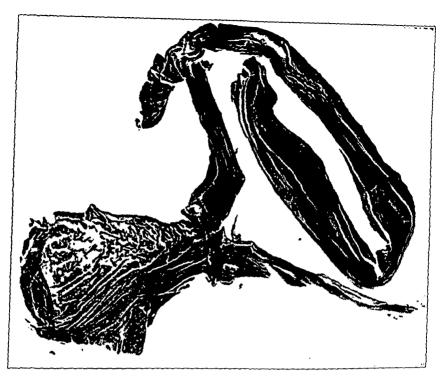
Fig. 4.—Three ileac ulcers, one walled off, one acute and one perforated, leading to peritonitis thirty-six days after gastro-ileostomy. The anastomosis is 15 cm. from the ileocecal valve.

Fig. 5.—Large chronic ileac ulcer with perforation (shown by black marker) seventy-four days after gastro-ileostomy.

TABLE 2.—*Gastro-Ileostomy*

Dog	Anasto-mosis from Ileocecal Valve, Cm.	Duration of Experiment, Days	Cause of Death; Autopsy Observations	Ulcer, Ileac	Blood Chlorides		Weight, kg.	
					Pre-opera-tively	Just Before Death	Pre-opera-tively	At Death
255	155	63	Peritonitis; perforated ulcer		404	446	10.8	7.0
229	136	74	Peritonitis; perforated ulcer	+	440	480	16.1	8.9
242	105	51	Peritonitis; perforated ulcer	+	452	370	9.0	3.8
813	115	58	Distemper; diffuse ileitis		478	474	12.8	11.0
36	78	8	Pneumonia; acute ileal ulcers; hemorrhagic colitis		476	377	18.2	14.8
907	53	26	Pneumonia; slight local peritonitis from perforated ulcer	+	468	492	6.4	3.8
471	48	60	Pneumonia; hemorrhagic colitis; 1 healed ulcer in ileum		490	352	24.6	14.4
476	25	6	Distemper; hemorrhagic colitis	0	...		16.9	15.1
146	18	3	Intestinal obstruction; hemorrhagic colitis	0	424	...	26.2	24.0
45	15	6	3 ileal ulcers (1 acute, 1 walled off, 1 perforated with peritonitis); hemorrhagic colitis	+	452	310	17.8	16.1

TABLE 3.—*Gastrocolostomy*

Dog	Anasto-mosis Distal to Ileocecal Valve, Cm.	Duration of Experiment, Days	Autopsy Observations	Hemor-rhagic Colitis	Blood Chlorides		Weight, Kg.	
					Pre-opera-tively	Just Before Death	Pre-opera-tively	At Death
987	10	20	Pneumonia; hemorrhagic colitis	+	454	316	28.8	20.8
990	8	4	Perianastomotic peritonitis; hemorrhagic colitis	+	750	405	16.2	13.6
469	12	9	Hemorrhagic ulceration of colon; gastric ulcer	+	459	274	17.9	13.8
693	18	5	Pneumonia; hemorrhagic colitis	+	420	...	18.0	15.2
11	15	4	Hemorrhagic colitis; 3 acute ulcers of colon	+	456	362	29.8	26.6
46	8	3	Hemorrhagic colitis	+	448	...	18.8	16.4
49	15	9	Hemorrhagic colitis; hemoglobin just prior to death, 45 mg. per 100 cc.	+	416	332	25.4	20.4
215	10	11	Hemorrhagic colitis; hemoglobin just prior to death, 40 mg. per 100 cc.	+	483	194	11.2	6.3
986	8	2	Slight local peritonitis	+	...	...	17.5	16.2
50	12	7	Anastomotic leak; local peritonitis; hemorrhagic colitis	+	462	230	22.9	14.0

40 and 45 per cent was noted in two dogs, and another had a hemoglobin reading of 50 per cent. Determinations of the blood chloride declined rapidly and in one case dropped to 40 per cent of the initial figure shortly before death. At autopsy marked hemorrhagic colitis with numerous superficial hemorrhages and erosions, as well as free blood in the lumen of the colon, was seen grossly in each case. The proximal half of the colon was involved only once in this severe case of colitis, while in the other cases, even though the anastomoses were in the proximal portion, there was no irritation near the stoma or in the proximal half of the large bowel. The colitis extended to the anus. Microscopic examination of the hemorrhagic areas showed many mucosal hemorrhages and small erosions. In one animal a large acute ulcer of the pyloric region of the stomach was encountered. Table 3 shows the results of this series.

COMMENT

Ivy and Fauley [2] and others found that there is a higher incidence of postoperative ulcer following end-to-end anastomosis of the stomach and small intestine than following end-to-side anastomosis. In my experiments only end-to-side unions were made. Also the pyloric sphincter was not included in the end of the stomach. Thus the increased motor drive normally exerted by the sphincter was absent. This minimized the factor of mechanical trauma in the formation of the ulcers. The anastomotic stoma was made large in order to obviate gastric retention, which is thought to increase gastric acidity and predispose to the formation of ulcers.

From the results of the experiments it appears that the acid gastric content was the most important etiologic factor in the formation of ulcer. No ulceration was noted in the duodenum after four gastroduodenostomies. In these experiments the acid content of the stomach was rapidly neutralized by the duodenal juices, the formation of ulcer thus being prevented. However, as the outlet of the stomach was placed at progressively lower levels in the intestines, the incidence of ulcer increased. This may be explained by an increasing sensitivity of the intestinal mucosa at progressively lower levels, by partial absorption of the neutralizing duodenal juices in the duodenum and the upper part of the jejunum, or by changes in the duodenal juices at lower levels in the intestine by which the neutralizing properties of the juices are greatly reduced. Even though the pyloric sphincter was absent at the anastomoses, which were made large, half of the ulcers in the small intestines occurred opposite the stoma. This fact lends some support to the theory of mechanical trauma as a factor in the production of

ulcers. McCann[17] and others considered mechanical factors important in their experimental ulcers.

Support is given to the acid theory of the formation of ulcer, in preference to the mechanical theory, by the condition in the duodenum and colon after operation. In the duodenum there were no ulcers, while in the colon, although practically no irritation was seen about the anastomoses, the distal portion was the seat of severe irritation. As the food which the animals ate was well ground before administration, the irritation in the colon cannot be entirely ascribed to trauma from "roughage."

If the outlet for the contents of the stomach was placed in the lower portion of the ileum or colon, the body weight and blood chlorides fell rapidly. This did not occur if the anastomosis was in approximately the upper two thirds of the small intestine, unless symptoms of ulcer developed, when it was noted that the weight fell, but the chlorides remained essentially normal.

The use of nonabsorbable suture material (linen) in half of the operations caused no mucosal irritation or formation of ulcer.

In a few of the autopsies food was found in the intestines proximal to the anastomosis, indicating a reverse peristalsis of the small intestines. Efforts were made in four experiments to show this reverse peristalsis by the administration of barium sulphate by stomach tube and roentgenologic study, but were unsuccessful.

SUMMARY

1. End-to-side anastomoses between the open pyloric end of the stomach and the progressively lower levels of the intestine from the duodenum to the colon, inclusive, were made in thirty-five dogs.

2. The intestinal mucosa was increasingly more sensitive to gastric content from the duodenum to the colon. No duodenal ulceration followed gastroduodenostomy. Jejunal ulceration was noted in five of eleven dogs (45 per cent). Ileac ulceration developed in eight of ten animals (80 per cent) after gastro-ileostomy. Each of ten dogs had marked hemorrhagic colitis subsequent to gastrocolostomy, and usually this led to secondary anemia. The mucosa of the distal half of the colon was much more sensitive to the acid gastric content than was that of the proximal half.

3. Following anastomosis of the stomach to the lower portion of the ileum or colon, the blood chlorides and the weight fell rapidly, and there was often a marked bloody diarrhea.

17. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

Fig. 10.—Rubber tubing was present at *a* but fell out in sectioning. It had been in contact with the blood vessel (*c*) of a rabbit for two days. At *b* is the granulocytic membrane. A few polymorphonuclear leukocytes are infiltrating the vessel wall; *d* is uncoagulated blood in the vessel.
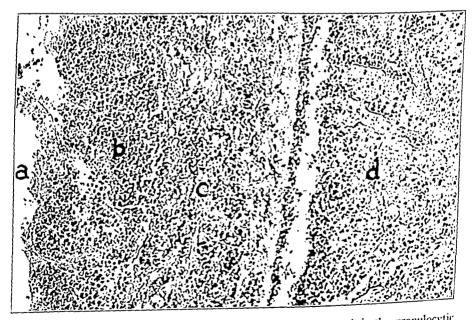
Fig. 11.—Rubber tubing was present at *a* for eight days; *b* is the granulocytic membrane; *c*, the vessel wall with early necrosis and marked infiltration of leukocytes; *d*, uncoagulated and degenerating blood. The specimen is from the neck of a rabbit.

Microscopic study of forty-eight hour specimens showed slight edema of the vessel walls. The blood within the vessel was beginning to organize as a healthy appearing thrombus. The organization extended from the wall where the gauze was in direct contact.

Nine day specimens showed the vessel filled with a rapidly organizing thrombus (fig. 12). Later stages showed a continuation of a healthy organizing process.

Ligation of a vessel may result in the rapid development of a thrombus near the point of ligation when the intima is injured, but uncoagulated blood may remain in the vessel for weeks if the intima is not traumatized in ligation.
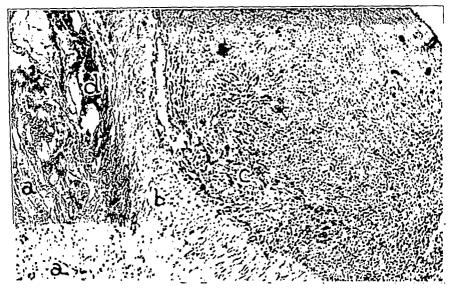
Fig. 12.—Specimen made by placing gauze in contact with a vessel in the neck of a rabbit for eight days. The gauze threads are at *a, a; b* shows a vessel wall; *c*, organizing blood clot firmly fixed to the intima of the vessel. The small lymph node at *d* is compressed by gauze against the vessel.

Hertzler demonstrated that if a mild chemical irritation was applied to the vessel wall, organization of the blood was stimulated. He also showed that application of violent irritation caused marked delay in organization, even though a clot was formed in the vessel.

Our experiments show the application of these principles in the relation of blood vessels to drainage material placed in a wound. The effect of failure of lymph spaces and small blood vessels to be sealed by coagulation in a fresh wound owing to the irritating effect of the rubber solution is readily understood. This causes an excess of serous and bloody discharge in clean wounds in which rubber tubing has been

used for drainage. Thus one may also explain the absence of this factor when gauze is used. The irritating effect of gauze is just sufficient to stimulate the development of fibrillar fibrin, with the result that blood and lymph vessels are effectively sealed.

There was a certain degree of damage to the vessel walls in contact with the rubber, in some cases amounting to actual necrosis. This required a number of days to become marked. The observation is of practical importance as it shows the easy possibility of secondary hemorrhage resulting from rupture of damaged vessels when rubber tubing has been allowed to come in contact with them over too long a period.

Space does not permit me to describe details of the behavior of tissue in the presence of some of the other more commonly used drainage materials. Scarcely any of them fail to produce a reaction. Even rubber dam is surrounded with a thin granulocytic membrane within two days after it is placed in a wound. Cellophane also produces a reaction, but one of almost negligible degree.

The discussion presented is not expected to serve as adequate direction for the handling of individual cases. It is only by study of the fundamental principles and their application to the task to be accomplished that one can expect to produce the most favorable results.

SUMMARY

1. Rubber tubing used for drains in wounds creates a granulocytic membrane on the wall of the wound where the rubber touches it, delaying healing.

2. The rubber tubing creates, by overstimulation of the tissue and by preventing coagulation, an excess amount of drainage not incident to the surgical procedure.

3. It should not be used as drainage material in clean wounds.

4. The manner of response of the tissue to rubber tubing may be an advantage in draining infected wounds.

5. In clean wounds gauze becomes fixed to the tissue after a few hours, but it is loose again in from six to eight days, and its removal is easy.

6. If the gauze is allowed to remain long past this time, it becomes firmly and permanently fixed in the tissue.

7. In clean wounds an ideal surface for rapid healing is left when the gauze is removed.

8. Rubber tubing delays formation of a thrombus in vessels, while gauze may promote it.

9. Rubber tubing may cause rupture of blood vessels if it is allowed to come in contact with them over too long a period.

OSTEODYSTROPHIA FIBROSA UNILATERALIS

REPORT OF A CASE

ERNST FREUND, M.D.
IOWA CITY

The case to be reported presents an unusual unilateral skeletal lesion which shows intimate relationship to Ollier's achondroplasia, from which it can, however, be differentiated roentgenologically, histologically and even clinically.

REPORT OF CASE

History.—The patient was a girl who came under clinical observation in 1926, at the age of 7 years. She began to limp on the left side in the spring of 1924. March, 1925, she fell to the floor and sustained a fracture of the left femur. She was taken to a hospital, where a diagnosis of bone tumor or cyst was made, based on roentgenograms. Solid bony union did not occur until March, 1926, following a period of traction and fixation in a plaster cast. The patient was symptomless except for an occasional dull pain in the region of the left hip, especially when the weather changed. When she was first seen in the clinic a diagnosis of osteitis fibrosa cystica of the upper end of the femur, with a healed pathologic fracture, was made. She did not report again until October, 1932, at which time her mother stated that the left leg had been bowing progressively. In the latter part of July, 1932, she fell hard on the left arm and had a dull pain at the junction of the upper and middle thirds of the humerus. The arm swelled one-third larger than its normal size. The swelling disappeared within one week, and the pain within two weeks. No physician was consulted.

The patient was a well developed and well nourished white girl (fig. 1), who walked on crutches because of a marked deformity of the left lower extremity. The most striking objective finding was the asymmetry of the face and extremities.

Head.—There was a slight but distinct asymmetry of the face, the left side being somewhat underdeveloped. The muscular action on the left side was slightly decreased, and the patient said that she "smiled higher" on the right side than on the left. The pupils were round, regular and equal and reacted to light and in accommodation. There was no difference in the vascularity of the two halves of the face, and blushing occurred in equal degree on both ears and both cheeks. The mouth, neck, chest and abdomen were not remarkable.

Left Upper Extremity.—The left arm was thicker than the right, and there was some anterior bowing at the middle of the humerus. Palpation revealed a more diffuse enlargement of the bone; there was no tenderness. The left forearm showed a similar swelling in its upper two-thirds. The left thumb was slightly larger in circumference than the right. There was free motion in all the joints. The skin was normal, and there was no difference between the skin temperature of the right and left sides. (The upper part of the left arm was ½ inch [1.3 cm.] longer than the right and almost 1 inch [2.5 cm.] thicker.)

Left Lower Extremity.—This was atrophic in toto and, owing to the marked deformity of the thigh, was shorter than the right lower extremity. At the junction of the upper and middle thirds a marked lateral and anterior bowing of the femur was present. The bone was palpable at this level as a hard, slightly irregular tumor mass without tenderness on pressure. There was valgus deformity in the region of the knee joint. The left tibia was increased in size in the upper half and showed anterior bowing in the middle. Active and passive motions in the knee and ankle joints were normal. In the hip joint adduction and abduction

Fig. 1.—Photograph of the patient, showing the marked deformity of the left lower extremity and the slight asymmetry of the face.

and external rotation were zero; flexion was normal, and there was internal rotation of 15 degrees. (The spinomalleolar distance was 31⅝ inches [80.3 cm.] on the right, and 30¼ inches [76.8 cm.] on the left. The left leg was ¾ inch [1.9 cm.] longer than the right leg.) All the other results of physical examination were negative.

Laboratory Findings.—The Wassermann and Kahn reactions were negative. The red blood corpuscles numbered 4,740,000, the white blood corpuscles 8,400. The chemical findings were as follows: serum calcium 11.1 mg.; serum phosphorus, 3.9 mg., and phosphatase, 32.5 mg. The urinary calcium on three successive days averaged 0.94 Gm. for twenty-four hours, and the urinary phosphorus, 1.061 Gm.

Roentgenologic Examination.—This also emphasized the unilaterality of the pathologic changes. The skull and spine and bones of the right extremities did not reveal pathologic changes. The left upper extremity showed no changes in the scapula and clavicle, but the left humerus (fig. 2) revealed definite hyperostotic-porotic changes involving almost the entire diaphysis. Only in the distal end and in the upper epiphysis could normal bone structure be seen. There was an almost uniform and equal thickening of the diaphysis. The cortical bone was markedly thinned out and formed only a very thin bony layer, which, however, in no place
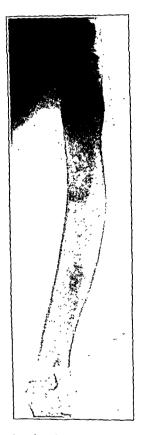
Fig. 2.—Roentgenogram showing hyperostotic-porotic changes in the diaphysis of the left humerus. The upper epiphysis and the distal end of the bone show normal structure; the rest of the bone is cloudy and porotic.

was completely interrupted. The surface of the diaphysis was smooth, and there were no signs of active apposition of periosteal bone. The shadow of the bone was cloudy and porotic; only in a few places could a definite structure be seen. These areas probably represented areas of spongy bone where the pathologic changes had not yet appeared. The picture was that of diffuse osteoporosis without cyst formation. In addition to the marked increase in thickness, the diaphysis also showed a distinct increase in length (¾ inch), despite some bowing at the middle third. There were no signs of a recent or healed fracture.

Left Forearm (figs. 3 and 4).—Lesions similar to that of the humerus were seen in the diaphysis of the left radius and in the bones of the thumb. The upper two thirds of the diaphysis of the radius were considerably enlarged and showed the same cloudy and porotic shadow as the humerus. A distinct line of demar-
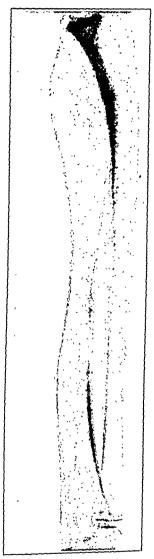
Fig. 3.—Roentgenogram of the left forearm, lateral view. The radius is considerably enlarged in its upper two-thirds; the distal third and the entire ulna are of normal structure.

cation between the middle and lower third separated the diseased from the healthy bone tissue. The epiphyses of the radius and the entire ulna did not show pathologic changes.

The bones of the wrist and of the four fingers were normal. The first metacarpal bone and both phalanges were uniformly and considerably thickened. The cortical bone was thinned out, and the shape was cylindric instead of biconcave. The diaphyses showed the same porotic shadow as the humerus and radius.

Left Lower Extremity.—The left femur (fig. 5) showed marked bowing of its upper end. The bone was thickened in its upper third, and the cortical bone on the outer side of the femur was markedly thinned out. The bone structure was irregular; osteoporotic changes were prevalent. There was an oblique line going
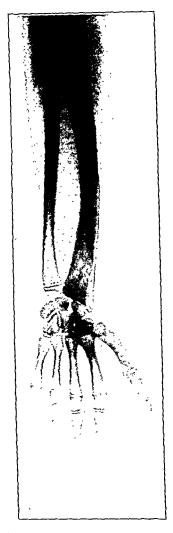
Fig. 4.—Anteroposterior view of the left forearm and hand. Only the radius and the bones of the thumb are involved.

downward and outward from the region of the lesser trochanter, representing probably the old fracture which was completely healed. The upper end of the femur showed the same cloudy shadow as the bones of the upper extremity. The greater trochanter and the proximal epiphysis had evidently been spared; they showed normal, although porotic, bone structure. Marked coxa vara was present; the greater trochanter almost touched the outer edge of the roof of the acetabulum (there were no intrinsic pathologic changes in the hip joint).

The diaphysis was involved in almost its entire length. There were differences in the bone structure at various levels of the femur. The cloudy porotic shadow of the upper portion has already been mentioned. The upper part of the distal fragment showed more irregularities, with areas of more pronounced osteosclerosis. These alternated with extensive areas of osteoporosis which showed

Fig. 5.—Roentgenogram of the markedly deformed left femur with irregular, mainly porotic, structure.

bony trabeculae and were free from the cloudiness seen in the upper fragment. Farther down the changes were almost purely porotic and were combined with slight enlargement of the femoral diaphysis. The distal third of the femur was less porotic, but here also the bony structure was completely changed; the normal spongy bone was replaced by a rather dense spotty and spongy mass which looked almost like cotton. The distal metaphysis and epiphysis showed normal but porotic structures.

The roentgenograms of the leg showed involvement of the tibia only (fig. 6). Almost the entire diaphysis showed the same hyperostotic porotic process which led to an increase of thickness and length (1½ inches [3.8 cm.] in the lateral view), resulting in bowing of the tibia. There was a marked valgus deformity at the junction of the middle and upper thirds. The distal third was involved
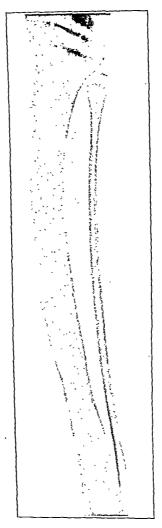
Fig. 6.—Anteroposterior view of the left leg; only the tibia is involved, with an increase in thickness and length.

to a lesser degree and was not enlarged. The cortex, although porotic, still seemed to be the old one. The spongy bone, however, had already been transformed and gave the same picture as the upper portion of the tibia.

The changes in the left foot corresponded to those in the left hand; the bones of the big toe only were involved (fig. 7). There was also some irregularity in

the bony structure of the first cuneiform bone and possibly of the scaphoid, but it was difficult to ascertain whether these changes were due only to atrophy resulting from disuse.

Biopsy.—For further information biopsy was performed (Oct. 27, 1932). A piece of bone was taken from the left tibia at the junction of the middle and lower thirds. Histologic examination revealed the following changes: The cortical bone was much thicker on the distal end of the specimen than on the proximal end; it was composed of rather compact lamellar bone with haversian canals.

Fig. 7.—Anteroposterior view of the left foot, showing involvement of the bones of the big toe, possibly of the scaphoid and first cuneiform bone.

These canals were enlarged by the osteoclastic resorption of bone, forming irregular marrow spaces with hyperemic fibrous bone marrow. The resorption of the old lamellar bone was followed by the formation of small trabeculae of fibrous bone tissue. Near the proximal end the old lamellar cortical bone had almost completely disappeared, and there was only a thin bony layer formed by the apposition of periosteal bone. Inside this layer a rather dense fibrous bone marrow was present, in which many thin trabeculae of primitive fibrous bone were embedded. The central portions were calcified; the superficial layers were osteoid. Near the endosteal surface of the cortex trabeculae of old lamellar bone were still present, which were lacunar in outline. Some of these fragments were

included in the central portion of primitive fibrous bone. The marrow spaces adjacent to the old cortex still showed fatty bone marrow with lamellar spongy bone, but in many places, especially along the vessels of the marrow, the fatty bone marrow had been replaced by fibrous tissue. This led to osteoclastic resorption of the old lamellar bone and to its replacement by fibrous spongy bone. The new spongy bone was without static arrangement. No cartilaginous tissue could be found.

Operation and Recovery.—Because of the histologic observations and roentgenologic findings, osteitis fibrosa von Recklinghausen was considered as a diagnosis, and an exploratory operation was performed on the parathyroid glands (Dr. Petersen, Nov. 23, 1932). No parathyroid tumor was encountered. The two lower parathyroid glands were removed. Histologically, they did not show pathologic changes. The patient made a normal recovery and was discharged for three months. On her return, in March, 1933, her general condition was found to be excellent. There were practically no changes in the local and chemical conditions or in the roentgenologic findings.

COMMENT

The findings in this case suggest that the condition was a systemic disease of the bones which involved the skeletal system unilaterally, but did not involve all the bones of the affected side. The involvement of the bones appears to have followed certain rules, as of the bones of the upper extremity only the humerus, radius and the bones of the thumb were affected. The left lower extremity showed in a similar way involvement of the femur, tibia and great toe. There was distinct asymmetry of the face, owing to underdevelopment of the left side. The unilateral aspect of the disease and the asymmetry of the face are more or less characteristic symptoms of Ollier's achondroplasia.

Ollier,[1] in 1899, described a definite disease of the bones characterized on roentgen examination by irregularity and delay of endochondral ossification. The epiphyseal cartilage does not undergo normal ossification, but preserves its structure and remains in the form of irregular cartilaginous masses which commonly require a long time to become ossified. These masses may be superficial or deep, subperiosteal or intramedullary. The phalanges of the toes, and especially those of the fingers, are sites of predilection. A part of the phalanx or the whole thickness may be involved. Ollier mentioned disseminated chondromas of the phalanges. In the long bones of the extremities near the epiphyseal plate osteochondromatous tumors are also found. They transform the juxta-epiphyseal portions into transparent, distended, voluminous masses. The epiphyses remain more cartilaginous and show less bone tissue than in normal persons. Ollier assumes that dyschondroplasia takes place on both sides of the epiphyseal plate. The irregularity of

1. Quoted by Frangenheim.[2]

ossification leads to a disturbance in length growth and in deformities. Ollier did not doubt the cartilaginous nature of the lesion, although he made no histologic examination.

Wittek,[1] in 1906, published a monograph on dyschondroplasia, with the report of one case. He concluded:

There is a congenital lesion of the cartilage of the epiphyseal disc consisting in a primary growth disturbance. As far as the long bones are concerned, this lesion is strictly unilateral. The first clinical symptoms become manifest in early childhood and lead to shortening of the extremity with tumor formation of the long bones at the epiphyseal plates. The tumors are chondromata; they consume during growth cartilaginous material which under physiological conditions would be used for length growth. The proliferation of cartilage occurs very irregularly in all directions, possibly the most in the direction of least resistance. The process leaves its strict unilaterality only at the distal ends of the extremities where it also changes its appearance. Here, the cartilaginous masses do not arise from the epiphyseal plate only but also from isolated particles of it. The disease is a characteristic symptom-complex and occupies a distinct position among the group of multiple chondromata.

Therefore, Wittek agreed with Ollier in considering the condition as a disease *sui generis*.

Frangenheim,[2] in 1911, and Hackenbroch,[3] in 1922, rejected the views held by Ollier and Wittek and considered dyschondroplasia in all cases as multiple chondromas. Frangenheim especially stated that he would perhaps consider dyschondroplasia as a new disease if there were really strict unilaterality. But in no case did he find the unilaterality persistent.

In the years following, many articles on Ollier's disease were written, and the number of unilateral cases reported in the literature amounts to about thirty. Some of these do not fulfil completely Fragenheim's postulates, but there are a number of cases of the strictly unilateral type. Thus there is no doubt of the existence of a unilateral disease of cartilaginous dystrophy (Ollier's disease) which histologically and roentgenologically is in intimate relationship with the group of multiple chondromas.

If one tries to place the case reported in this article in the category of Ollier's achondroplasia one meets with some difficulties. Apart from the unilaterality and the asymmetry of the face (a frequent but by no means constant symptom in Ollier's disease), there are a number of differences between this case and those reported in the literature.

2. Frangenheim, P.: Chondromatose des Skeletts, Beitr. z. klin. Chir. **73**: 226, 1911.

3. Hackenbroch, M.: Ollier'sche Wachstumsstörung: Chondromatose des Skeletts, Arch. f. orthop. Chir. **21**:206, 1922; Ueber Ollier'sche Wachstumsstörung und Chondromatose des Skeletts, Fortschr. a. d. Geb. d. Röntgenstrahlen **30**:432, 1922-1923.

In Ollier's disease the clinical signs become noticeable within the first year of life or soon after the child walks. The first sign is usually deformity of the extremities combined with shortening. My patient was, according to her mother, perfectly well until her fifth year. At that time she began to limp and soon after sustained a pathologic fracture. The fracture healed slowly, with marked deformity, and since that time the patient had shown progressive changes in the bones. It is possible that changes in the bones were present before the clinical signs were manifest, but this is only a supposition, and it is doubtful whether the disease started very long before the clinical signs appeared.

Another outstanding feature of Ollier's disease is shortening of the affected extremities. This is not only an apparent shortening caused by deformities but a real one and is due to an intrinsic disturbance of the endochondral ossification. My patient showed shortening of the left lower extremity, but this was only apparent owing to the deformity caused by the fracture. The tibia and humerus, however, showed a definite increase in length, so that the tibia, which was fastened at both ends to a perfectly normal fibula, showed marked anterior bowing.

Furthermore, there are marked differences between the roentgenograms of my patient and those of patients with Ollier's disease. Ollier's disease resembles roentgenologically enchondromatosis of the skeleton. A coarse structure is seen in the region of the metaphyses, with irregular strands, enlarged areas of rarefaction, through which a few long bony trabeculae run. The rarefied areas represent clear spaces which frequently contain small dense nodular shadows; these are often conglomerate. The affected metaphyses usually show a clublike enlargement, with thinning of, and even defect in, the cortex. Practically all investigators agree that the transparent irregular masses are formed in the metaphyses. Flotow [4] stated that he was almost always able to find in the roentgenograms a bridgelike formation running from the epiphyseal plate toward the chondromatous metaphyses. In long bones in which there is involvement of both metaphyses, the central portion of the diaphyses often shows normal bone tissue. The changes in the epiphyses are less marked; deformities and delaying ossification, however, are frequently described.

The most striking feature in the roentgenograms in my case is that the pathologic changes occurred only in the diaphyses; the epiphyses and the epiphyseal plates were apparently not involved in the process. The metaphyses may or may not have shown pathologic bone structure. One does not get the impression that the process started primarily in the metaphyses or directly in the epiphyseal plate. In these respects

4. Flotow, F.: Ueber den Halbseitentyp der Chondromatose, Ztschr. f. orthop. Chir. **51**:505, 1929.

this case differs from one of Ollier's disease, and even more so in regard to the bone structure and the configuration of the involved diaphyses. The clublike enlargement by a transparent irregularly nodular tumor mass was not present, but there was a more diffuse widening of the diaphysis, with a cloudy porotic osseous shadow. There were no circumscribed areas of rarefaction or small spotty, dense shadows of calcification. There was no "blowing up" of the cortex with defect, but the cortex, which was in most places extremely porotic, was rather straight and preserved its continuity.

Finally, the biopsy in this case gave a histologic picture which is quite unlike that of Ollier's disease. All the investigators who performed biopsy in cases of Ollier's disease reported enchondroma and mature hyaline cartilaginous tissue with or without calcification. The specimen removed from the left tibia of my patient, at the level separating the diseased from the normal bone, showed the typical picture of osteitis fibrosa.

Thus the clinical and roentgenologic findings and histologic observations speak against the diagnosis of Ollier's disease. The most important fact is the histologic observation which points toward the diagnosis of osteitis fibrosa. Before further discussion of the relationship to Ollier's disease, the significance of the histologic diagnosis of osteitis fibrosa in this case must be considered.

It is necessary, however, to emphasize that the histologic picture of osteitis fibrosa has no specific significance. Histologically, one can have the identical picture in Recklinghausen's disease, in osteitis fibrosa localisata, even in some areas in Paget's disease, in osteomalacia and rickets, in chronic inflammatory diseases of the bone marrow, in cases of fracture with callus formation and in other conditions. Therefore, one must admit that a diagnosis based only on histologic examination of a relatively small piece of bone is usually insufficient and may lead to great error. Unlike examination of the parenchymatous organs, a single slide in diseases of the bones may disguise more than it reveals. In diseases of the bones histologic examination can be of value only if different bones on many sections have been carefully examined.

On this basis the osteitis fibrosa in the case reported might possibly be interpreted as an accidental finding, a form of reaction of the bone marrow to a lesion of another type not contained in the specimen. It is theoretically possible that the bone marrow near a chondroma may show fibrosis, with new bone formation, and so a final diagnosis of osteitis fibrosa would be inadequate and misleading. But I do not think that such skepticism would be justified in this case. The biopsy specimen was taken at a level where roentgenologically healthy bone tissue was invaded by the pathologic process. The diseased portion showed, however, the same irregular cloudy and porotic shadow seen in all the other
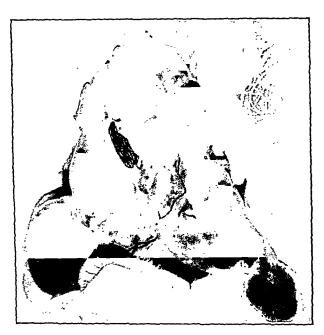
Fig. 2.—Gallbladder, extrahepatic biliary ducts and duodenum on examination with filtered ultraviolet radiation after the intravenous injection of 2 per cent mercurochrome.

Female Genital Tract.—Enough of a 2 per cent solution of aqueous eosin was injected into the bicornate uterus of a living rabbit to distend it. With slight pressure, the dye passed over into the fallopian tubes. Under filtered ultraviolet radiation the uterus and tubes were golden yellow. During the injection some of the dye spilled over into the abdominal cavity through the fimbriated ends of the tubes, producing a visual Rubin test. The ease with which the tubes fluoresced in the rabbit suggested the investigation of the genital system of man. Injections were made through the rigid external os of the cervix into the genital system of a girl, aged 14, obtained at autopsy. On incision, the uterus showed intense staining of the endometrium with deep penetration of the dye into the muscular coat. When watery eosin was injected into the lumen of the fallopian tube at the uterotubal junction, a strong golden fluorescence of the tube was noted, and with the increased pressure of the injection at the junction, the dye diffused throughout the broad ligament, so that it became a golden sheet. It is well known that a thick-walled tube will not be effectively visualized; however, if the dye reaches the tubal lumen it will be possible to observe the emission or nonemission of the dye from the fimbriated end. An attempt is being made to produce a nontoxic fluorescent iodized poppy-seed oil. This will enable the visualization under fluorescence of what the radiograph demonstrates, provided the fallopian tubes are not thickened.[3]

Urinary Tract.—When a 2 per cent solution of aqueous eosin was injected into the lumen of a ureter of a living or dead rabbit (downward toward the bladder), a fine stream of dye passed through the ureteral orifice; on irradiation of the opened urinary bladder, a fine golden stream of dye was seen, and the ureteral orifices were stained a golden yellow. When the dye was injected toward the pelvis of the kidney (pyelovenous backflow), the pelvis was filled if enough dye was used; with sufficient pressure, rupture through the calices into the kidney substance occurred.[4]

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3. It may be noted that Hauser (Strahlentherapie **33**:582, 1929) observed a red fluorescence in all forms of vaginal hemorrhage, whether normal, as in menstruation, or abnormal. This is the only reference we can find on the use of filtered ultraviolet light in gynecology.

4. Hadjioloff and Kresteff (Compt. rend. Soc. de biol. **106**:662, 1931) studied the fluorescence of urine in higher and lower vertebrates. They believed that the yellow fluorescence of urine is due either to urochrome or to urobilin, though the problem may be complicated by the presence of microbic and ferment factors. The intensity and color of urine apparently vary with the species. True (Compt. rend. Soc. de biol. **99**:1847, 1928) devised a fluorescent method of testing renal permeability by the injection of a 0.5 per cent solution of acriflavine hydrochloride in animals; the solution is excreted by the kidneys within thirty minutes and fluoresces a yellow-green. The substance, it is noted, is eliminated unequally by the urinary tubules and is not shown in the glomeruli. In man, the dye appears in the urine first within fifteen minutes after injection and remains there for thirty-six hours. The *p*ₙ of the urine has no bearing on the fluorescent reaction.

The ureter showed only a golden fluorescence when distended with aqueous eosin.

Bronchial Tree.—The direct injection of a 2 per cent watery solution of eosin into the trachea of a dead rabbit caused a visualization of the trachea and its branches, down to the very finest terminal bronchioles; it was noted, however, that the injection of the finer bronchioles was irregular, mucous plugs apparently blocking the further passage of the dye. The uncut surface of the lung showed golden, triangular, infarct-like areas, corresponding to the segments in which patent bronchioles allowed the passage of the dye. A fluorescent iodized poppy-seed oil would be of great aid in the visualization of the bronchi and the alveoli in the opened thorax by means of filtered ultraviolet radiation.

Esophagus.—Direct injection of a 2 per cent solution of aqueous eosin into the esophagus of a dead rabbit gave excellent fluorescence of that organ, especially when it was temporarily clamped off at its gastric end.

VISUALIZATION OF THE ARTERIAL TREE

After investigating the visualization by filtered ultraviolet radiation of tubular and hollow organs in the rabbit following the intravenous or direct injection of eosin or mercurochrome, it was decided to study the visualization of the arterial tree in the same animal.

The injection by a syringe of 50 cc. of a 2 per cent watery solution of eosin or mercurochrome into the abdominal aorta of a dead rabbit which had been exsanguinated before death disseminated the dye widely through the vascular channels of the body. Under the action of filtered ultraviolet radiation, which with eosin or mercurochrome produces a strong, golden-yellow fluorescence, the entire arterial system was delineated, as if dissected in gold. The actual outlining of the course of the vessels under this radiation permitted much easier dissection than with the naked eye. The venous channels were not colored, and the veins fluoresced a dark brown because of their large content of clotted blood. Examination of the vascular tree should be conducted at once, since the dye diffuses into the adjacent tissues. During the course of the injection, the gastric, mesenteric, intestinal and splenic arteries were observed with the naked eye to color, but under radiation the vessels fluoresced a rich golden yellow, which extended to the finest ramifications. The use of a hand lens enabled more detailed study.

The coronary arteries of the heart of a rabbit which had received injections were well outlined, and some vessels in the endocardium were visible. The myocardium showed no vessels. The parietal pericardial vessels were also stained. The kidneys showed pin-point vascular markings in the cortex; the medulla was at first free from fluorescence but

became fluorescent later by diffusion. The ureter could be traced by the fluorescence of the periureteric vessels. The urinary bladder showed fine vascular markings in its mucosa. In the dead animal, after an intra-aortic injection of the dye, the gallbladder and the extrahepatic vessels showed up well. The vascular outlines of the mesenteric, intestinal, gastric and splenic arteries, especially the finer serous ramifications of the former, were as stated earlier, well defined. Diffusion took place rapidly in the serosa of the stomach and intestine. The serous vessels about the fallopian tubes were diffusely injected, so that they appeared as golden yellow tubes. The dura of the brain and spinal cord, as well as the arachnoid layer, showed marked diffuse injection, though the cortex of the brain and the substance of the spinal cord did not stain.[5]

Subcutaneous vessels showed diffusely through the unopened skin in many areas. The intercostal vessels in the opened thorax could be fully traced. The major and minor vessels in the arteriovascular tree of the upper and lower extremities could be distinctly followed. Thus, about the knee joint, the median superior geniculate artery was easily seen. The infrapatellar fat and the synovia were also stained golden. The muscular and periosteal vessels were visible. Neither marrow nor cartilage fluoresced a golden color, in either the living or the dead animal. If the dye was injected directly into the bone marrow of a dead animal, the dye could not be demonstrated, owing to the diffuse, dark appearance of hemoglobin. Prolonged soaking of the marrow in the eosin ultimately colored it.

This method may be used for demonstrating the arteriovascular system in part or as a whole, though it is to be remembered that the distinct outline of the finer vessels is lost by diffusion within an hour after injection. Eosin in liquid petrolatum or eosinated beeswax [6] may be used in more permanent preparations. Fixation of a particular region may be accomplished by the use of a 2 per cent solution of eosin in a 10 per cent solution of formaldehyde (4 per cent solution of formalde-

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5. Study of the literature indicates that some attention has been paid to the fluorescence of cerebrospinal fluid. Thus Exner (Psychiat.-neurol. Wchnschr. **32:** 218, 1930), who noted that normal spinal fluid fluoresces a deep violet under ultraviolet radiation, studied the alterations of the fluorescence of the fluid in nervous diseases. Schaltenbrand and Putnam (Deutsche Ztschr. f. Nerven. **96:**123, 1927), in an excellent study of the circulation of the cerebrospinal fluid, noted that a 10 per cent solution of fluorescein injected into the blood stream in live animals is demonstrated in the cerebrospinal fluid within fifteen minutes. They did not use filtered ultraviolet radiation in their study.

6. Eosin in liquid petrolatum or beeswax may be prepared by the use of a common solvent, such as cedar oil or xylol, with incubation of the solution for from about thirty to sixty minutes, to insure an even spread of the dye in the petrolatum or beeswax.

hyde U. S. P.). We are uncertain just how long the fluorescence of the finer vessels will last by the latter two methods.

In the living animal, however, the arteriovascular tree was visualized after intra-aortic injection of larger doses of eosin. The dye was excreted by the biliary system and the kidneys, although if large amounts were injected the mesenteric and intestinal vessels showed the dye. The vascular tree of the extremities in a living animal may be visualized by this method if the arterial and venous circulations are retarded temporarily by a tourniquet. When the dye was injected into the beating heart, no particular fluorescence of the heart or the coronary vessels occurred. When the dye was injected into the inferior vena cava of a living animal under pressure in the direction of the liver, a retrograde flow of blood was accomplished, and under sufficient pressure the surface and substance of the liver became finely lobulated by dye markings. Under the radiation the borders of these lobules were outlined in gold. When a frozen section was made of a piece of liver eosin was found both in the central and in the interlobular veins. With release of pressure, the flow of blood became normal again, and the dye was propelled toward the heart. A sample of blood withdrawn from the inferior vena cava gave the characteristic golden color, though the inferior vena cava itself did not fluoresce golden but brown.

No dye was noted in the anterior chamber of the eye after the death of the animal. Other body fluids were not tested.[7]

Modifications and variants of this method could be tried. Thus, for instance, certain phases of placental relations could be investigated in both living and dead animals. The method may be useful in the study of the lymphatic system, since many dyes are transported by the lymphatics. It may also be used to detect minute quantities of dyes in

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7. Ehrlich (quoted by Kramer, in Virchows Arch. f. path. Anat. **274**:215, 1930) noted that fluorescein, which is the mother substance of eosin and mercurochrome, is distributed in the body fluids and is not taken up by fat or brain tissue. Schaltenbrand and Putnam noted the extensive distribution of 10 per cent solution of fluorescein, injected into the blood stream, in the skin, mucosae, muscle, connective tissue and dura mater and in various secretions such as the fluid of the anterior chamber of the eye and the cerebrospinal fluid. They pointed out that the substance of the central nervous system is not affected and that no change is noted in vessels, either in the wall or in the lumen. The oral administration of eosin (Rost, quoted by Kramer) gave no local or general effects. Kramer and Tappeiner (quoted also by Kramer) studied the effects of subcutaneous injections of eosin in animals. Tappeiner also injected the dye intravenously. Binet and Fabre (J. de pharm. et chim. **9**:16, 1929) injected olive oil, rendered fluorescent by the addition of di-phenylanthracene, into the blood stream and studied the distribution of this fluorescent oil in various organs. The lung is noted as having the greatest lipopexic powers. Di-phenylanthracene fluoresces blue and was demonstrated in various proportions in the blood from different organs and tissues.

cavities and fluids of the body. Fluorescent dyes which are so diluted that they are imperceptible by unaided vision are easily detected by filtered ultraviolet radiation.

SUMMARY

A method for the examination of tubular organs by the injection of aqueous eosin or medicinal mercurochrome is proposed. With the use of filtered ultraviolet radiation, many of the tubular organs fluoresce a golden yellow. Similarly, the injection of aqueous eosin or medicinal mercurochrome into the aorta of a dead animal shows the arterial system as golden tubes on examination with ultraviolet radiation.

SPINA BIFIDA AND CRANIUM BIFIDUM

A STUDY OF ONE HUNDRED AND THREE CASES

SIDNEY W. GROSS, M.D.*

AND

ERNEST SACHS, M.D.

ST. LOUIS

INTRODUCTION

The problem of spina bifida has occupied the attention of surgeons for many years, and, in spite of a voluminous literature that has accumulated on the subject, fundamental differences of opinion still exist. Excellent contributions on the anatomy of spina bifida have been made by von Recklinghausen.[1] Keiller[2] and others;[3] however, the underlying factors in the pathogenesis of this condition have not been determined. Many theories have been advanced, but convincing proof of any of them is still lacking. One of us (E. S.) has always felt that hyperactivity of the choroid plexuses in utero before the neural arches have completely closed was a probable cause of the condition. The fact that the choroid plexuses are formed, according to Hochstetter,[4] before the

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1. von Recklinghausen, F.: Untersuchungen über die Spina Bifida, Virchows Arch. f. path. Anat. **105**:243, 1886.
2. Keiller, V. H.: A Contribution to the Anatomy of Spina Bifida, Brain **45**:31, 1922.
3. Tourneux and Martin: L'histoire du spina bifida, J. de l'anat. et physiol. **17**:1, 1884. Fischel, A.: Ueber Anomalien des zentralen Nervensystems bei jungen menschlichen Embryonen, Beitr. z. path. Anat. u. z. allg. Path. **41**:536, 1907.
4. Hochstetter, F.: Ueber die Entwickelung der Plexus chorioidei der Seitenkammern des menschlichen Gehirns, Anat. Anz. **45**:225, 1913.

neural arches are closed[5] makes this possible, but no embryologic or experimental proof exists for this theory.

A complete review of the literature would lead to needless reduplication. We have, therefore, selected a few papers which we believe bring out the significant points concerning this subject. In considering the surgical aspect, we have chosen those reports of cases in which a considerable number of the operations were performed in one clinic, and have omitted entirely such elaborate studies as that of the Clinical Society of London,[6] for, though this study reveals many interesting facts, its value from a surgical standpoint is small, since many of the cases were observed when modern surgical methods were still in their infancy.
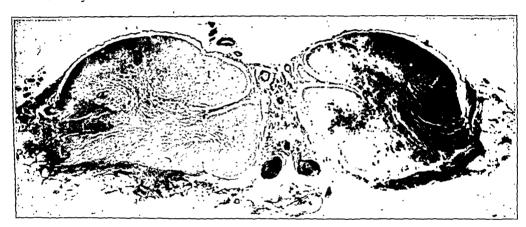
Fig. 1.—Section of a double spinal cord.

The occurrence of associated developmental defects of the central nervous system in cases of spina bifida has been pointed out by other observers. It is of importance in determining the prognosis in this group of cases. This point was therefore investigated. Of 29 cases that came to autopsy (no operation, 19; operation, 10), 8 showed marked defects. Six cases showed hydromyelocele. (Keiller[2] found this condition in 3 of 7 cases of spina bifida studied post mortem.) In 1 case a cleft extended along the entire dorsal aspect of the spinal cord, and in another, there was a double cord below the site of the spina bifida (fig. 1). In about 25 per cent of the cases which came to autopsy, a defect was present in addition to the spina bifida; however, 19 of these

5. Bardeen, C. R.: Manual of Human Embryology, edited by F. Keibel and F. P. Mall, Philadelphia, J. B. Lippincott Company, 1910, vol. 1.

6. Tr. Clin. Soc., London **18**:339, 1885.

cases, or about 66 per cent, were considered inoperable on account of the condition of the spina bifida. This factor, therefore, would seem to play a small rôle in establishing operative indications.

REVIEW OF LITERATURE

Surgeons may be divided into two groups in regard to their views on operation: Those who favor operation at an early age, and those who take the attitude expressed in Frazier's [7] book, that operation should be delayed until the patient is a year or more old, except when rupture of the sac is imminent. While it is true that operations performed on infants more than a year old result in a much lower mortality, it must be remembered that many of the deaths might have been prevented by early operation. The mortality of children with spina bifida who are not operated on is appalling. In the report of the Clinical Society of London,[6] in 1885, 615 of 647 deaths from spina bifida occurred in infants less than 1 year of age. Consequently, the mortality of 35 per cent reported by Moore [8] in a series of 385 cases (gathered from the literature) in children who were operated on when less than 1 year of age is not excessive. Harmer,[9] in 1917, reported a mortality of 40 per cent in a series of 34 cases in which he performed operation. In this series there were 7 patients with meningocele, 23 with myelomeningocele and 4 with cranium bifidum. Twenty-two of the patients had ulcerated or leaking sacs, and of these only 9 survived. Cutler,[10] at the Children's Hospital in Boston, analyzed 39 cases in which operation was performed. The youngest patient was 18 hours old and the oldest, 3 years. In this group there were 15 patients with simple meningocele and 24 with myelomeningocele. Thirteen of the patients had ruptured or granulating sacs. The mortality was 41 per cent. Of the patients who were discharged from the hospital, the end-result in 6 was unknown; 7 were living and well, 1 was living and improved, 4 were living but had complications and 4 had died. Of 18 patients on whom operation was not performed, 10 had died; the result in 6 was unknown, and 2 were alive.

In a recent contribution on the subject, Penfield and Cone [11] suggested a "new method" for the plastic repair of meningocele and

7. Frazier, C. H.: Survey of the Spine and Spinal Cord, New York, D. Appleton and Company, 1918, p. 265.

8. Moore, J. E.: Spina Bifida: With a Report of Three Hundred and Eighty-five Cases Treated by Excision, Surg., Gynec. & Obst. **1**:137, 1905.

9. Harmer, T. W.: Spina Bifida and Allied Malformations, Boston M. & S. J. **177**:353, 1917.

10. Cutler, G. D.: End-Results in Sixty-Two Cases of Spina Bifida and Cephalocele, Arch. Neurol. & Psychiat. **12**:149 (Aug.) 1924.

11. Penfield, W., and Cone, W.: Spina Bifida and Cranium Bifidum: Results of Plastic Repair of Meningocele and Myelomeningocele by a New Method, J. A. M. A. **98**:454 (Feb. 6) 1932.

myelomeningocele. They attempt to conserve the sac, because in the histologic study of excised meningocele sacs they have found cell nests which resemble the arachnoidal collections in the pacchionian granulations, and which they believe serve as an absorbing mechanism for the excess cerebrospinal fluid. In their series of 19 cases there was not a single death, and in no instance did hydrocephalus develop, yet in the protocols they stated that "in 4 cases noticeably large heads developed." We wonder if ventricular puncture in these 4 cases might not have shown hydrocephalus.

The preservation of the sac was suggested in 1902 by Schmidt.[12] He did not open the sac freely, but merely emptied it by puncture, involuted it and used it to fill the bony defect. In the 3 cases which he reported, the results were good.

Since there is such a divergence of opinion, it seemed desirable to collect and analyze, and to determine the results in, all cases observed in one clinic over a long period of time (twenty years) during which these cases were handled under similar conditions, and one definite policy was followed. From such a series it would seem one might draw some definite conclusions and determine the best policy to pursue.

CLINICAL MATERIAL

The present report is based on a study of 103 cases. Of these, there were 96 cases of spina bifida in infants or young children and 5 cases of cranium bifidum. The latter are included since the problem of treatment is very similar. Two cases of spina bifida occulta in young adults who presented neurologic symptoms are also included. All cases of spina bifida in which there was some function in the lower extremities and in which there was no pronounced hydrocephalus were considered suitable for operation, which was undertaken as soon as the patient's condition warranted it. If, at the time of the patient's admission, the spina bifida was ulcerated, the ulcerated area was treated until it was covered by epithelium. In some of the cases seen in the early part of the twenty year period, we operated in the presence of ulceration, but experience showed us that no matter how we prepared the area of operation, it was practically impossible to secure a clean operative field, so that today operation is delayed until the area is completely epithelialized.

ANALYSIS OF CASES

Cases in which Operation was not Performed.—Forty-six of the patients in this series were not subjected to operation. Of these, 36 died while in the hospital. Of the 10 who survived, 6 had extensive

12. Schmidt, G. B.: Ueber die Radikaloperation der Spina Bifida. Beitr. z. klin. Chir. **34**:351, 1902.

defects (rachischisis, a hopeless condition), associated with hydrocephalus and complete paralysis of the lower extremities; 4 had leaking and infected sacs and were taken from the hospital by the parents against advice while attempts were being made to secure a clean operative field. Of the 36 patients who died in the hospital, 23 were afflicted with hydrocephalus and paralysis of the lower extremities, and 1 had complete paralysis of both lower extremities without hydrocephalus. In all but 4 cases, the covering of the defect was ulcerated. Postmortem examination was done in 19 of the 36 fatal cases. The causes of death were: meningitis and hydrocephalus, 9 cases; pneumonia and hydrocephalus, 4; pyelonephritis and hydrocephalus, 3; pyelonephritis, 1; pneumonia, 1, and otitis media and hydrocephalus, 1.

It is significant that of the 19 cases that came to autopsy, hydrocephalus was present in all but 2. In addition, hydrocephalus was found clinically in 7 of the 17 cases in which an autopsy was not permitted. The causes of death in this group were: meningitis, 9 cases; pneumonia, 5; otitis media, 1, and unknown, 2.

Cases in Which Operation Was Performed.—Fifty-seven patients were subjected to operation. Twenty had simple meningocele; 27, myelomeningocele; 3, syringomyelomeningocele; 5, cranium bifidum with meningocele in 4 and myelomeningocele in 1, and 2 (adults), spina bifida occulta with disturbances of the bladder and trophic lesions of the feet. In this series, 43 of the patients with spina bifida and 4 with cranium bifidum were less than 1 year of age when operation was performed. Of the group with spina bifida, 3 were operated on during the first week of life. Ten were from 1 to 4 weeks old; 18, from 1 to 3 months old; 5, from 3 to 6 months old; 7, from 6 to 12 months old and 7, 1 year or older. Of the 20 simple meningoceles, 15 occurred in the lumbosacral region, 3 in the dorsal region and 2 in the cervical region. Of the 27 myelomeningoceles, 24 were in the lumbosacral region and 3 in the dorsal region. The 3 syringomyelomeningoceles occurred in the lumbar region.

The 50 cases of spina bifida have been divided into two groups: those in which operation was performed before 1927 and those in which operation was performed after that date. The reason for this apparent arbitrary division is that in the past five years our results have been so much better than in the previous fifteen years. This, we believe, is to be accounted for by the fact that our method of treatment in the second period had become fairly well standardized, and a much better method of closing the defects in the skin was employed. Experience and improvement in technic were undoubtedly also factors in this change, but the most important factor, we believe, was the extensive mobilization of the skin for a considerable distance on all sides of the defect before a closure was attempted.

INDICATIONS FOR OPERATION

In electing cases suitable for operation, the following points were considered:

1. In all cases of spina bifida the epithelial covering must be intact. If at the time of the patient's admission the surface was ulcerated, treatment was given until the surface became epithelialized.

2. Some movement must be present in at least one lower extremity, but it was not essential that all movements be present. There must, however, be enough movements so that when the infant grew up transplantation of muscles or stabilization of the joints could be done or braces could be worn.

3. Hydrocephalus, if present, must not be extreme. The degree of hydrocephalus was not judged by any definite measurements, but by the rate at which the head had been enlarging and by the width of the open sutures. The mere presence of hydrocephalus, however, was not considered a contraindication, for, though the treatment is vastly more complicated when one also has to deal with hydrocephalus, it is not an insurmountable problem. A question of grave importance which we are unable to answer definitely is, How large may an internal hydrocephalus be without causing mental impairment and to what extent do dilated ventricles return to normal? On the latter point, we have one important observation. Following the removal of a cerebellar tumor in a patient with dilated ventricles, ventriculographic studies were made which showed that the ventricles were greatly reduced in size and were practically normal.

4. Absence of control of the bladder, when it could be determined, was not a contraindication for operation. In a number of instances disturbances of the bladder caused us much concern when the child grew up, and some of the children have had to wear urinals. We have never transplanted ureters or performed any operation to correct this condition, though it has been discussed on a number of occasions with urologists.

5. The presence of deformities of the lower extremities, such as club feet, were not considered contraindications if the legs were sufficiently developed to permit of corrective orthopedic measures.

Of the 20 patients with simple meningocele, 2 showed evidence of hydrocephalus prior to operation, and only 2 presented evidence of weakness of the lower extremities.

Twelve of the 27 patients with myelomeningocele presented evidence of hydrocephalus before operation and 12 showed some degree of motor and sensory disturbances in the lower extremities. The correct diagnosis was not made before operation on the 3 patients with syringo-

myelomeningocele. Two of these showed evidence of hydrocephalus, and the third, paralysis of both lower extremities prior to operation.

Two adults who complained of urinary incontinence were found to have spina bifida occulta. One patient also had trophic ulcers of both feet. Laminectomy was done in both cases in an effort to alleviate the symptoms.

Congenital defects of the skull and cerebral meninges occur much less frequently than defects of the spine. In our series of 103 cases, there were 5 of cranium bifidum. All of the patients were treated surgically. The distribution in these cases was as follows: occipital meningocele in 2 infants, occipital myelomeningocele with associated hydrocephalus in 1 infant, frontal meningocele in 1 infant and meningocele at the vertex of the skull in a 6 year old girl.
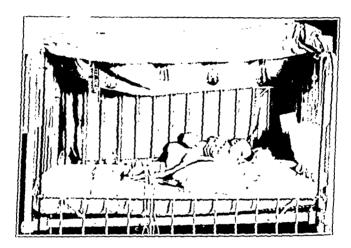
Fig. 2.—Heated crib for the preoperative and the postoperative care of infants. The canvas sides can be lowered and the temperature varied by turning on more of the electric lights. The straps that hold the baby's feet can be adjusted so that the legs are kept apart and the stool drops down between the legs.

METHOD OF TREATMENT

Preoperative Care.—Infants with spina bifida tolerate operation well if certain precautions are observed. No operation is undertaken until the pediatrician has determined that the patient is tolerating his food and is in the best condition from a nutritional standpoint. Each infant is kept in a crib with a tent about it which is heated with electric light bulbs, the temperature being kept at from 95 to 98 F. (fig. 2). The child wears no clothing and no diaper and is kept lying on its abdomen on a pillow so that the legs hang down. There is no dressing over the spina bifida. The purpose of these precautions is to prevent injury to the spina bifida and all soiling of the operative field with urine or feces, which greatly increases the danger of postoperative infection. Infants tolerate these operations well if they do not lose body heat and fluid. Consequently before operation the infant receives 200 or 250 cc. of saline solution subcutaneously; then as much
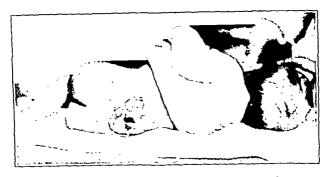
Fig. 3. (M. K., table 2).—Infant with myelomeningocele.
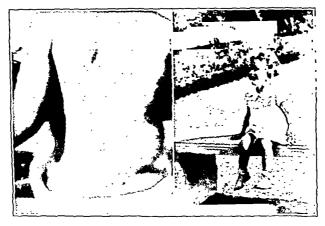
Fig. 4.—The patient in figure 3, after removal of the myelomeningocele. The small picture, taken when the child was 3 years of age, shows the droop foot, for which she wears a shoe with a right angle stop.

Fig. 5.—Cranium bifidum before and after operation.

of the infant's body is wrapped in cotton as a wide exposure of the operative field permits, and the operation is performed on a heated table. A minimal amount of ether is given, and the anesthesia is never started until the patient has been draped and the operator is standing at the table ready to begin.

Fig. 6.—Cranium bifidum before operation.

Fig. 7.—The patient shown in figure 6, after operation.

Operative Procedure.—The operation is performed in the following steps: The sac is dissected out, and the neck of the sac is exposed all around the defect in the spine. The sac is then opened, and all nerve elements are freed and replaced in the spinal canal, after meticulous hemostasis. Enough of the sac is retained to close the defect comfortably with interrupted silk sutures, without tension. We have never found any reason for attempting to save every bit of the sac, as sug-

gested recently by Penfield and Cone.[11] To fill the canal with all this excess of tissue may cause pressure on the roots. Penfield believes that saving the wall of the sac prevents the development of hydrocephalus, but in our experience this does not occur after operation as frequently as has been supposed, though one can never tell beforehand in which case it may appear. One or two flaps of the fascia of the erector spinae muscles are cut and tacked over the defect.

Then there follows what frequently is the most important and difficult part of the operation—providing ample cutaneous and subcutaneous covering for the defect. We have tried various ways of doing this, and no universal rule can be laid down for all cases, but, in the vast majority, mobilization of the skin and subcutaneous tissue for a great distance, not infrequently well forward on the lateral portion of the abdomen, is the most satisfactory procedure. Swinging pedicle flaps is not as satisfactory as the danger of a little necrosis at the edge of the flap is too great. Unfortunately, it is not feasible as a· rule to make a pedicle flap according to the method of Blair, that is, cutting the flap first and moving it later.

TABLE 1.—*Follow-Up Results on Ten Patients Operated on for Myelomeningocele*

Initials	Age at Operation	Age at Time of Follow-Up	Comment
J. C.	3½ mos.	3 yrs.	Seems normal in every respect, except for slight enuresis
B. K.	4 yrs.	6 yrs.	Spastic paraplegia when operated on, no improvement
D. K.	7 days	1 yr.	Child very healthy; has club feet which are being treated
D. T.	8 mos.	5 yrs.	Walks with braces; seems normal mentally
H. A.	7 wks.	1 yr.	Slight hydrocephalus
J. M.	3 wks.	2 yrs.	Walks with braces; mentally normal
Don K.	5 wks.	3 yrs.	Healthy except for recurrent urinary infections
M. K. (figs. 3 and 4)	5 wks.	3 yrs.	Walks with braces; is still getting corrective orthopedic treatment
A. P.	19 mos.	7 yrs.	Weakness of both lower extremities; incontinence
R. F.	3 mos.	15 mos.	Seems normal

Postoperative Care.—After the operation, the child is kept on its abdomen in the enclosed heated crib until the wound is healed. Careful measurements of the size of the head and the tenseness of the fontanels are made. Fluids are restricted if there is a tendency for the head to enlarge.

FOLLOW-UP RESULTS

Since end-results are of vital importance in a study of this type, an effort was made to get in touch with all the patients on whom operation was performed. Of the 38 patients who were discharged from the hospital, answers were received concerning 26.

Of the 26, 11 had had simple meningocele; 10 of these were well in every respect and 1 child (D. H.) who had had a high dorsal meningocele was in good health but was said to show slight awkwardness in using his fingers.

Of the remaining 15 patients, 12 had had myelomeningocele; 2 of these died from an undetermined cause shortly after discharge from the hospital. The results in the remaining 10 are shown in table 1. Of

the 4 patients with cranium bifidum and associated meningocele, follow-up records were available on 3. All were living and in good health (figs. 5, 6 and 7).

TABLE 2.—*Data on Patients Operated on Between 1912 and 1927*

Initials and Sex*	Date and Age	Type	Hydro-cephalus	Paralysis	Resulting Hydro-cephalus	Immediate Results	Comment
M. O. ♀	7/19/12 8 yrs.	Lumbar meningocele	No	Club feet; awkward gait	No	Not improved	Incontinence
C. B. ♀	9/19/14 3 mos.	Myelomeningocele	Slight	No	Yes	Poor	Infection of wound
R. B. ♂	1/6/16 10 days	Syringomyelocele; coverings ulcerated	Yes	No	Yes	Died	Meningitis 2 wks. after operation
R. D. ♂	2/16/16 6 wks.	Myelomeningocele; coverings ulcerated	Yes	Complete, both lower extremities	....	Died	Meningitis 3 wks. after operation
P. H. ♂	9/7/18 5 wks.	Dorsal (fourth and fifth) myelomeningocele	No	No	No	Good	
C. S. ♀	2/5/19 10 mos.	Myelomeningocele	No	No	No	Died	Pyelonephritis 3 wks. after operation
R. F. ♀	9/18/19 3 mos.	Myelomeningocele	No	Both lower extremities	No	Good	Seen 1 yr. later; uses legs satisfactorily
A. P. ♀	11/3/19 1 yr., 7 mos.	Myelomeningocele	Slight	No	No increase in hydro-cephalus	Weakness of both legs after operation	Seen 5 yrs. later, cauda equina syndrome
A. H. ♀	12/19/19 6 days	Meningocele; coverings ulcerated	No	No	No	Infection of wound	Infection on admission
L. J. ♀	3/24/20 7 mos.	Meningocele	No	No	....	Died	Pneumonia third day after operation
L. R. ♂	6/21/20 11 mos.	Meningocele with dermoid cyst	No	No	No	Good	
W. J. ♂	9/28/21 8 mos.	Dorsal meningocele	Yes	No	Increased	Choroido-plexectomy 2 wks. later	Death third day after operation
B. S. ♀	12/6/22 3 wks.	Meningocele	Slight	No	Increased	Died	Pneumonia; increasing hydro-cephalus
B. D. ♂	9/5/23 16 days	Myelomeningocele	No	No	Yes	Choroido-plexectomy at 5½ wks.	Died same day
B. J. ♀	10/5/23 7 days	Dorsal meningocele	No	No	No	Good	
K. D. ♂	12/11/24 6 wks.	Myelomeningocele; sac infected	No	No	Yes	Died	Pneumonia and basilar meningitis at 7 wks.
B. E. ♂	11/9/25 2 wks.	Lumbar meningocele	No	No	No	Good	Seen at 2 yrs.; child normal
C. E. ♀	1/9/25 19 mos.	Syringomyelocele	Yes	Lower extremities	....	Died	Death 2 hrs. after operation
L. W. ♀	5/12/25 1 mo.	Myelomeningocele	No	No	No	Improved	Mild meningitis developed; recovery
A. F. ♀	7/11/26 7 mos.	Low dorsal and lumbar syringomyelocele	No	No	....	Died	Death on first day after operation

* In this column, ♂ indicates male; ♀, female.

COMMENT

The mortality following operation in cases of spina bifida and cranium bifidum, according to the literature, has ranged between 40 and 50 per cent when the operations were performed early in life.

TABLE 3.—*Data on Patients Operated on Between 1927 and 1932*

Initials and Sex*	Date and Age	Type	Hydro-cephalus	Paralysis	Resulting Hydro-cephalus	Immediate Results	Comment
D. T. ♀	3/28/27 8 mos.	Lumbar meningo-myelocele	Yes	Both lower extremities	No increase	Good	Follow-up in 5 yrs.; walks with brace; incontinence
B. G. ♀	5/19/27 2 mos.	Myelomeningocele; infected sac	Yes	Both lower extremities spastic	....	Died: meningitis	
B. B. ♀	6/ 5/27 3 mos.	Low dorsal myelo-meningocele	Yes	No	Increase in hydro-cephalus	Poor	Died after a few weeks at home
D. K. ♂	3/21/27 5 wks.	Myelomeningocele	No	No	No	Good	Seen 3 yrs. later; urinary infection
D. H. ♂	10/15/27 3 yrs.	High dorsal men-ingocele	No	Both lower extremities; bilateral ankle clonus	No	Excellent	Follow-up in 5 yrs.; cured; walks
W. W. ♂	12/30/27 3 wks.	Myelomeningocele	Yes	Both lower extremities	Yes	Poor	Seen at 18 mos.; club feet; trophic ulcers
J. H. ♀	10/25/27 5½ mos.	Myelomeningocele	No	No	No	Good	Died 11/13/27; cause unknown
M. Z. ♀	5/31/28 8 mos.	Cervical meningo-cele	No	No	No	Good	
R. H. ♀	8/14/29 2½ mos.	Myelomeningocele	Yes	Partial	....	Died	Hyperthermia 30 hrs. after operation
C. F. ♀	7/11/29 2 yrs., 4 mos.	Myelomeningocele	No	Both lower extremities	No	Good	Power in legs increasing
J. B. ♂	10/8/29 1 mo.	Meningocele	No	No	No	Good	Letter 2/10/33 stating "He is very healthy"
J. R. ♀	9/ 8/29 5 wks.	Meningocele	No	No	No	Good	Sac invaginated into canal; normal 3 yrs. later
L. H. ♀	11/1/29 2 mos.	Cervical meningo-cele	No	No	No	Good	Follow-up 2/14/33; normal in every way
A. W. ♀	11/9/29 2 mos.	Meningocele	No	No	No	Died	
J. M. ♂	11/21/29 3 wks.	Myelomeningocele	No	Weakness of lower extremities	No	Improved	Follow-up 2/24/31; extremities stronger; walks with braces
J. C. ♀	9/21/30 3½ mos.	Myelomeningocele	Yes	No	Slight increase	Same	Follow-up 2/14/33; "seems normal in every way"
M. M. ♀	9/21/28 2 mos.	Myelomeningocele	Slight	Lower extremity	....	Died	Death 2 wks. after operation
B. C. ♂	3/10/30 6 wks.	Myelomeningocele	Yes	Both lower extremities	Increase in hydro-cephalus	Died	Pneumonia 4 wks. after operation
M. K. ♀ (fig. 3 and 4)	4/28/30 5 wks.	Myelomeningocele	No	Right foot	No	Good	Follow-up Nov., 1932; excellent health; walks with braces
B. C. ♂	5/ 7/30 10 days	Myelomeningocele	No	No	No	Good	
L. W. ♀	11/20/30 2 mos.	Meningocele	No	No	No	Good	
J. D. ♀	11/30/30 1 yr.	Meningocele	No	No	No	Good	Child normal at 3 yrs.
E. J. ♂	1/28/31 3 mos.	Meningocele	No	No	No	Good	Follow-up 2/21/33; "perfect in every way"
F. R. ♂	2/ 9/31 4 mos.	Meningocele	No	No	No	Good	Follow-up 2/24/33; "normal in every way"

* In this column, ♂ indicates male; ♀, female.

TABLE 3.—*Data on Patients Operated on Between 1927 and 1932—Continued*

Initials and Sex	Date and Age	Type	Hydro-cephalus	Paralysis	Resulting Hydro-cephalus	Immediate Results	Comment
B. K. ♀	5/15/31 4 yrs.	Myelomeningocele	No	Sensory loss below second dorsal ver-tebrae; spastic paraplegia	No	Same	Follow-up 2/16/33; no change in condi-tion; still has spastic para-plegia
H. A. ♀	11/27/31 7 wks.	Myelomeningocele	No	No	Slight	Poor ?	Follow-up Oct., 1932; has slight hydrocephalus
D. K. ♀	1/ 6/32 7 days	Myelomeningocele	No	No	No	Good	Child is well ex-cept for club feet
W. B. ♂	4/20/23 2 mos.	Meningocele with sacral teratoma	No	No	No	Good	Follow-up 2/16/33; "baby getting along just fine"
N. E. ♀	5/11/32 2 wks.	Meningocele	No	No	No	Good	Follow-up 2/11/33; "in very good health"
P. M. ♂	5/ 2/32 3 mos.	Dorsal myelo-meningocele	Slight	No	....	Died	Hyperthermia

Recently Penfield and Cone [11] reported 21 cases in which operation was performed with only 2 deaths, and Coughlin,[13] 12 cases with 1 death. In our own series, operation was performed in 50 cases of spina bifida with 14 deaths and in 5 cases of cranium bifidum with 1 death, a mortality of 27 per cent. Forty-seven of our patients were less than 1 year old. Because of the marked improvement in results since 1927, we divided our cases of spina bifida into two groups. Table 2 includes data on those cases in which operation was performed from 1912 to 1927. In this group there were 20 cases of spina bifida with 8 deaths (40 per cent mortality); in addition, in 2 of the cases a marked degree of hydrocephalus developed for which choroidoplexectomy was done with subsequent fatality. In table 3 are presented data on the cases in which operation was performed during the second period (from 1927 to 1932). There were 30 cases of spina bifida in this group with 6 deaths, a mortality of 20 per cent. As stated before, the marked improvement in the results since 1927 was due to several factors; how-ever, it is significant that of the 8 patients who died prior to 1927, 3 had infected sacs at the time of operation and died subsequently of meningitis. Since 1927, only 1 patient (B. G., table 3) with an infected sac has been operated on, and the fatality was also due to meningitis. The data in the cases of cranium bifidum are listed in table 4.

The frequency with which hydrocephalus developed after the repair of a spina bifida is indicated in the tables. In patients with simple

13. Coughlin, W. T.: Spina Bifida: A Clinical Study with a Report of Twelve Personal Cases, Ann. Surg. **94**:892, 1931.

meningocele, this was relatively uncommon. Of 20 patients, 2 had a mild degree of hydrocephalus before operation which increased following the repair of the spina bifida. Weakness of the lower extremities occurred only twice in patients with simple meningocele. In a child of 3 years (D. H., table 3), with a high dorsal meningocele, there was a bilateral ankle clonus and inability to walk. Five years after operation the child walked normally and was pronounced "cured" by the family physician. In cases in which nerve tissue was present in the sac, the incidence of hydrocephalus and paralysis of the lower extremities before and after operation was much greater than in cases with simple meningocele. Of 27 patients with myelomeningocele, 10 were afflicted with some degree of hydrocephalus prior to operation. Following repair of the spina bifida, the hydrocephalus increased in 5; in 2 there was no

TABLE 4.—*Data on Patients with Cranium Bifidum*

Initials and Sex*	Date and Age	Type	Hydrocephalus	Resulting Hydrocephalus	Immediate Result	Comment
A. H. ♀	5/ 9/21 3 mos.	Occipital meningocele	No	No	Good	Infant seen at 9 mos. of age; seemed normal
S. D. ♀	2/ 3/26 6 yrs.	Meningocele at vertex	No	No	Good	
G. R. ♀	4/20/27 3 days	Occipital myelomeningocele	Slight hydrocephalus	...	Died 5 wks. after operation	Necropsy showed absence of median lobe of cerebellum
H. K. ♀	1/27/27 12 days	Frontal meningocele	No	No	Good	Follow-up 2/27/33; "baby perfect"
L. G. H. ♂	10/20/30 6 mos.	Occipital meningocele	No	No	Good	Follow-up 2/16/33; "he is just fine"

* In this column, ♂ indicates male; ♀, female.

change, and the remaining 3 died shortly after operation. In 2 infants in whom enlargement of the head was not noted prior to operation hydrocephalus developed after repair of the spina bifida. It is interesting to note that in the group of 46 patients who were not operated on, 29 had hydrocephalus. Weakness of the lower extremities was present prior to operation in 10 patients with myelomeningocele. An improvement in the strength of the lower extremities followed operation in 5 cases; there was no improvement in 2, and death occurred shortly after operation in 3.

Of the 2 adults who were subjected to laminectomy because of neurologic symptoms associated with spina bifida occulta, 1 showed marked improvement in the control of the bladder and the trophic ulcers promptly healed. The second patient showed no improvement.

Five patients with cranium bifidum (table 4) were included in this study because of the marked similarity of this defect to spina bifida. The operative procedure in each case was similar to that employed in the repair of spina bifida. Four patients made satisfactory recoveries

without sequelae or complications. One infant, 3 days old, died five weeks after operation. Autopsy revealed complete absence of the median lobe of the cerebellum and a slight internal hydrocephalus. In addition, bronchopneumonia and acute purulent ependymitis were present.

SUMMARY

1. Fifty cases of spina bifida and 5 cases of cranium bifidum in which surgical treatment was carried out in one clinic have been analyzed.

2. Of 22 patients who were operated on before 1927, 10 died; of 33 operated on since 1927, only 6 died.

3. Patients with simple meningocele rarely have hydrocephalus or paralysis of the lower extremities prior to operation, and the follow-up histories obtained in 14 cases (11 cases of spina bifida with meningocele and 3 cases of cranium bifidum with meningocele) indicate that these children grow up normally following operation and rarely have any permanent serious disability.

4. When nerve tissue is present in the sac (cases with myelomeningocele or syringomyelomeningocele), however, hydrocephalus and weakness of the lower extremities are a frequent complication prior to operation. Though these symptoms persist, it is rather striking that the general idea that hydrocephalus will develop, even if it is not present before operation, does not seem to be supported by our experience. The conclusion that the type of closure is responsible for postoperative hydrocephalus does not seem justified.

In our series, almost 50 per cent of the patients developed normally (12 of 22).

HISTOLOGIC STUDIES OF AUTOGENOUS AND HOMOGENOUS TRANSPLANTS OF THE KIDNEY

P. P. T. WU, M.D.

Fellow in Experimental Surgery, the Mayo Foundation

AND

FRANK C. MANN, M.D.

Professor of Experimental Surgery, the Mayo Foundation

ROCHESTER, MINN.

An autogenous transplant of the kidney will function normally or maintain the life of the animal for several months or years. On the other hand, a homogenous transplant of the kidney will excrete urine for only a limited period and then rather abruptly cease to function. This peculiarity in the behavior of the homogenous transplant has been variously explained, but without the support of any definite evidence explanations can at best be purely hypothetic. Although it seems obvious that some light might be shed on the subject by knowledge of the histologic changes which take place in a homogenous transplanted kidney both before and after it has failed to excrete urine, such data are yet to be obtained.

The purpose of this investigation is to study the histologic changes that take place in the transplanted kidneys from day to day and to note any qualitative or quantitative difference in the kaleidoscopic picture between the autogenous and the homogenous types of transplants, as well as between the functioning and the nonfunctioning homotransplants.

SUMMARY OF THE LITERATURE

Autogenous transplants of the kidney have been found normal in size, color, consistence and microscopic appearance three weeks,[1] twenty-five days,[2] seventy-nine days and almost a year after operation.[3] On

1. Capelle: Ueber Dauerresultate nach Gefäss- und Organtransplantationen. Berl. klin. Wchnschr. **45**:2012 (Nov. 9) 1908. Stich, Rudolf: Zur Transplantation von Organen mittelst Gefässnaht. Arch. f. klin. Chir. **83**:494, 1907.

2. Lobenhoffer, Wilhelm: Funktionsprüfungen an transplantierten Nieren, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:197, 1913

3. Carrel, Alexis: Doppelte Nephrektomie und Reimplantation einer Niere, Arch. f. klin. Chir. **88**:379, 1909.

the other hand, Carrel,[4] Lobenhoffer,[2] Lurz,[5] Williamson[6] and Holloway[7] observed certain definite anatomic changes which accompanied the physiologic and pathologic processes prevailing in the transplanted organ. During the first few days, the microscopic pictures were such as would be expected after manipulating the organ, severing all the nerves and temporarily interrupting the circulation. No alteration in the histologic appearance took place until the function began to fail. Finally, the usual picture of hydronephrosis and infection prevailed.

In the case of the homogenous transplants, the kidneys have been found to be more or less normal two, twelve, fifty, seventy-one[8] and thirty-five days after homotransplantation.[9] However, these experiences are extraordinary. Usually, the homotransplants are subject to a great variety of lesions. Areas of infarction have been observed after the first or second day.[10] Partial or complete necrosis or gangrene of the kidney has taken place after forty hours,[11] one to eight days,[12] from five to eight days,[10] ten days or less [13] and from fourteen to eighteen days.[14] Calcification of the necrosed tubules has been noted after eighteen days. Absorption of the renal substance may begin on the fifteenth [10] day and be completed in three months.[13] The organ has been seen to become fibrosed in seventy-four days.[13] Hydronephrosis has been known to develop in six and fourteen days.[9]

Soon after transplantation, the homogenous kidney presents the microscopic picture of nephrosis. The glomeruli are normal. Desqua-

4. Carrel, Alexis: Remote Results of the Replantation of the Kidney and the Spleen, J. Exper. Med. **12**:146, 1910; footnote 3.

5. Lurz, L.: Ueber Nierentransplantationen: Vergleichende Untersuchungen des Urins und der Uretertätigkeit der autotransplantierten und der normalen Niere, Deutsche Ztschr. f. Chir. **194**:25, 1925.

6. Williamson, C. S.: Further Studies on the Transplantation of the Kidney, J. Urol. **16**:231, 1926.

7. Holloway, J. K.: The Effect of Diuretics on the Transplanted Kidneys, J. Urol. **15**:111, 1926.

8. Avramovici, Aurel: Les transplantations du rein (étude expérimentale), Lyon chir. **21**:734 (Nov.-Dec.) 1924.

9. Carrel, Alexis: Transplantation in Mass of the Kidneys, J. Exper. Med. **10**:98, 1908.

10. Mantelli, Candido: Esperienze sul trapianto dei reni, Pathologica **5**:69 (Feb. 1) 1913.

11. Decastello, A. V.: Ueber experimentelle Nierentransplantation, Wien. klin. Wchnschr. **15**:317 (March 20) 1902.

12. Floresco, N.: Recherches sur la transplantation du rein, J. de physiol. et de path. gén. **7**:47, 1905.

13. Villard, E., and Perrin, E.: Transplantations rénales, Lyon chir. **10**:109 (Aug. 1) 1913.

14. Borst and Enderlen: Ueber Transplantation von Gefässen und ganzen Organen, Deutsche Ztschr. f. Chir. **99**:54, 1909.

mation of the epithelial cells takes place. Coarse granulation and fatty degeneration affect the tubular epithelium, particularly that of the proximal convoluted tubules and the thick limbs of Henle's loops. Many of the thin limbs of Henle's loops and the collecting tubules contain casts.[15]

When the transplant was functioning more or less well, Williamson found a moderate amount of edema of the tubules. Occasionally some hyalin-like material was present in the collecting tubules. Ibuka noted cloudy swelling or degeneration of the renal parenchyma of varying degree. Shortly afterward, Williamson noticed early changes in the glomeruli and some lymphocytic infiltration with little alteration in the tubular elements. Then the glomeruli became more intensely congested, sometimes with the diapedesis of an erythrocyte into the capsular spaces. The swelling of the epithelial cells lining the tubules increased; the nuclei stained poorly, and occasionally actual degeneration was evident. A few polymorphonuclear leukocytes also appeared at this stage. Ibuka [15] observed progressive injury to the glomeruli and the tubules, represented in the extreme by fatty degeneration of the capillary tufts of the glomeruli and necrosis of the tubular epithelium.

As the functional life of the transplant comes to an end either a predominating glomerular type of injury or overwhelming tubular lesions prevail, depending on whether the process of failure is rapid or relatively slow. When ascending infection supervenes, abscesses, rarely cortical in distribution, may be formed and replacement of the renal parenchyma by fibrous tissue may take place.[6]

MATERIALS AND METHODS OF STUDY

For this study, twenty-four transplantations of the kidney were performed. Six of these composed a series of autogenous transplantations of the kidney, and they served as controls for another series of eighteen homogenous transplantations of the kidney.

Sixty biopsies were made. The specimens were fixed in Zenker's solution as soon as they were obtained. Three kinds of stains were used, hematoxylin and eosin, Mallory's phosphotungstic acid and hematoxylin and van Gieson's alum-hematoxylin, trinitrophenol and acid fuchsin. A total of one hundred and eighty sections was studied.

Medium-sized, short-haired, quiet dogs were selected. In the case of homotransplantation, the host and the donor were selected at random without any particular reference to their breed, sex or age. The animals were maintained on the regular kennel diet consisting of biscuits, milk, syrup and water, and an occasional allowance of meat. Unless the excretion from the transplanted kidney was

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15. Ibuka, Kenji: Function of the Homogenous Kidney Transplant. Am. J. M. Sc. **171**:420, 1926.

unusually profuse, 10 cc. of a 10 per cent solution of dextrose in physiologic solution of sodium chloride per kilogram of body weight was generally administered by the intravenous route just prior to the time for the collection of a preoperative specimen of urine.

The function of the transplanted kidney was estimated quantitatively by the results of chemical analyses of its excretion. As the general condition of the animal, the kind and amount of food and fluid intake, the details of the operation and environmental factors varied from day to day, the absolute values were of little significance without a certain standard of comparison. The function of the normal kidney in the case of autotransplantation and that of the host's kidneys in the case of homotransplantation served as such a criterion.

Every day immediately preceding the biopsy operation, a specimen of urine was collected from the transplant, and another one was obtained simultaneously by catheterization from the bladder. The concentrations of urea and ammonia nitrogen and creatinine in the urine were determined by the colorimetric methods of Folin and that of sodium chloride by the titration method of Whitehorn.

The operative procedures included transplantation and biopsy every twenty-four hours thereafter. All the operations were performed under ether anesthesia and with the strictest aseptic precautions. The operative field was shaved and washed with soap and water. It was then cleansed with a fat solvent and painted with two coats of a 2 per cent solution of iodine in benzene. Twenty-day 00 chromic catgut was used for suturing the muscles and the subcutaneous fascia, and linen for suturing the peritoneum and the skin. At the conclusion of the operation both the abdominal and the cervical wound were painted with iodine, and a dressing of collodion gauze was applied on the former and not on the latter.

Transplantation.—The sequence of the main events in transplantation consisted of: (1) the choice of a kidney as the transplant, (2) the preparation of the vessels in the neck for suturing, (3) nephrectomy and (4) vascular anastomoses. Except for the fact that two animals, a host and a donor, were used in homotransplantation, the technic was entirely the same for both varieties of transplantation.

Choice of a Kidney: A median line incision of the abdomen was made. The left kidney was mobilized by detachment from the surrounding fascia and ligaments, care being taken to leave the renal capsule intact. The renal vessels were isolated and examined. When it was found that the renal artery bifurcated close to its origin or that two separate renal arteries arose from the aorta, the right kidney had to be used.

Preparation of the Vessels in the Neck: A median line incision was made in the neck. Either side of the neck may be used. The common carotid artery was exposed, and a pocket to receive the transplant was made by separating the muscle by blunt dissection. The vessel was isolated and its adventitia removed for a distance of from 5 to 6 cm. A bull-dog clamp with padded blades was applied to the proximal end of the segment and a hemostat clamp to the distal end. The segment was divided with a sharp knife about 1 cm. above the proximal clamp. The distal end was ligated with linen and the portion proximal to the clamp excised. Any adventitia remaining attached to the proximal end of the vessel was then removed. Liquid petrolatum was applied to both sides of the vessel wall. A sponge saturated in warm saline solution was placed over it until the time to make the anastomosis.

The external jugular vein was prepared in a similar manner. The proximal end was then carried mesially through the fascia beneath the sternocleidomastoid muscle and placed under a sponge moistened with warm saline solution.

Nephrectomy: Two large curved clamps were applied on both the renal artery and the renal vein close to their origin from the aorta and the vena cava, respectively. The artery was clamped before the vein. The vessels were severed distal to the clamps. The ureter was freed and cut, with two thirds of it attached to the kidney. The kidney was not perfused. It was wrapped in a pack dipped in warm saline solution and was gently pressed between the hands.

When the transplantation of the kidney was completed, the renal vessels were doubly ligated with linen, and the abdominal wound was closed.

Vascular Anastomosis: After removal of the adventitia from the renal vessels the ends were cut even. The kidney was rotated 180 degrees on its long axis and placed on its convex border. The carotid artery was anastomosed to the renal artery before the external jugular vein was anastomosed to the renal vein.

Three sutures of 000 silk on straight number 16 needles were passed through both the media and the intima of the prepared ends of the vessels at points equidistant from one another. The ends of the vessels were brought together, and after the sutures were tied and held under a moderate amount of tension the vessels assumed a triangular shape. By rotation, first one side and then the other was held in the horizontal plane and sewed with a continuous through-and-through suture. One needle and suture was used for each side or for all three sides and tied to the next so-called stay suture.

After the anastomosis had been completed, first the clamp on the external jugular vein and then that on the common carotid artery were removed. Any bleeding from the suture line usually ceased after the application of digital pressure or heat, and occasionally after repair with one or two additional sutures.

The time when the first clamp was applied to the renal artery and the time when the clamp was removed from the common carotid artery were always noted. During that interval there was no circulation of blood through the kidney.

A catheter of suitable size was inserted into the ureter until the upper end reached the pelviureteral juncture. The distal end of the ureter was tied to hold the catheter in place as well as to stop bleeding from the ureteral vessels. The ureter was then passed under the sternocleidomastoid muscle and brought out through a stab wound in the skin on the other side of the neck. About 2 cm. of the ureteral stump was allowed to protrude beyond the surface of the skin and was held snugly in a tunnel formed by suturing the skin over it.

Biopsy.—For biopsies, the general surgical procedures remained essentially the same. The wound of the primary operation in the neck was opened. The transplanted kidney was freed from the surrounding tissues and lifted out of the muscle pocket. The artery was compressed by digital pressure, while a wedge-shaped piece of tissue, 2 by 1 by 0.5 cm., was excised from the convex border of the kidney. The specimen for the first biopsy was removed from midway between the two poles, and subsequently it was obtained from one side and then from the other alternately. The sites were so spaced as to include between them at least 1 cm. of renal substance.

The biopsy wound was closed with number 2 twenty-day chromic catgut by the use of two deeply placed interrupted mattress sutures and a superficial layer of continuous suture. The mattress sutures were knotted on opposite sides. For the first suture, the end carrying a number 8 long straight needle was cut short, whereas for the second, the reverse was done. For the continuous layer, the

suture was passed diagonally across the wound, first laterally to one extremity of the line of excision, then mesially to the center and finally laterally again to the other extremity, returning each time straight through the renal substance to the same side. At the conclusion it was tied to the end of the first mattress suture which was left long on the other side.

RESULTS OF INVESTIGATION

General Observations.—Of a total of twenty-four transplantations of the kidney, six were failures from the point of view of this study. Thrombosis in the renal vessels with infarction and necrosis of the kidney within twenty-four hours after transplantation occurred once in the autotransplantation series and twice in the homotransplantation series. One dog died before the operation of homotransplantation was completed, and another dog died of hemorrhage in less than a day after the transplantation of a homogenous kidney. In the sixth dog the transplanted kidney showed marked arteriosclerotic changes.

On the average it took an hour and fifty-six minutes to perform an autotransplantation and an hour and twenty-seven minutes to do a homotransplantation. The time which elapsed before the circulation through the transplanted kidney could be restored was thirty-two and a half minutes in the autotransplantation series, and twenty-seven and a half minutes in the homotransplantation series.

Three of the autogenous transplants of the kidney and six of the homotransplants functioned well during the entire period of observation, ranging from two to five days for the former and from one to five days for the latter. Two autotransplants functioned for two of three days, and one homotransplant functioned satisfactorily for only one of five days. Seven other homogenous transplants failed to excrete urine at any time. In these cases exploration revealed no thrombosis in the renal vessels. The biopsy wounds bled freely and healed well.

The average duration of the functional activity was seventy-two hours for the whole series of autogenous transplants and thirty-one hours for homogenous transplants. Leaving the nonfunctioning group out of consideration, we found that the homogenous transplants functioned for an average of fifty-eight hours.

So far as the results of urinalysis were concerned, there was no significant difference between the two varieties of transplants. The urine was generally pale. It was neutral or alkaline in reaction. Albuminuria was constant, although the quantity varied from a trace to a large amount. The sediment obtained after centrifugation contained a varying number of hyaline and granular casts, pus cells and erythrocytes. The concentration of urea and ammonia nitrogen and creatinine occasionally attained a high level but never equaled or exceeded that found in the urine of the normal kidney or kidneys. With few excep-

tions, the transplant secreted a far greater amount of sodium chloride per cubic centimeter of urine than the normal kidney or kidneys.

In the group of five autogenous transplants the experiment was terminated by death in four animals and by thrombosis in the renal vessels in one. In the group of thirteen experiments on homotransplantation the experiment was terminated by death in one animal and by thrombosis in the renal artery or vein, or both, in seven. In the remaining five experiments the transplanted kidney was purposely removed at operation.

The amount of serosanguineous exudate around the transplant in the muscle pocket and the intensity of the inflammatory reaction of the surrounding tissues and the overlying skin varied considerably. The general impression, however, was that they were much greater in the case of the homogenous than in the case of the autogenous transplants.

Histologic Observations.—The results of the experiments will be considered in three groups: (1) autogenous transplants; (2) functioning homogenous transplants, and (3) nonfunctioning homogenous transplants. The essential histologic observations and the complete protocols of the most representative experiment in each group are as follows:

Autogenous Transplants: The glomeruli were normal. Sometimes there was an albuminoid material in a few capsular spaces. The tubules at times appeared normal for the first one or two days and then revealed swelling and granular degeneration or hyalinization to a varying extent; or at times they showed the degenerative changes in the beginning and, after one or two days, either proceeded to hyalinize or resumed a more normal appearance. A varying number of tubules generally contained an albuminoid material in their lumens. In association with extensive polymorphonuclear leukocytic infiltration or necrosis, the content at times was cellular. A small number of tubules showed more or less dilatation of their lumens on the fourth and fifth days. The interstitial tissue generally showed only a few small areas of congestion or an occasional collection of mononuclear cells throughout the period of observation. Occasionally, however, it showed a progressively increasing amount of congestion and mononuclear cellular infiltration. In two experiments there was polymorphonuclear leukocytic infiltration with or without necrosis on the second day. In one of those cases, a large portion of the renal parenchyma was found to have been destroyed on the third day. The capsule of the kidney usually showed a varying amount of extravasation, formation of fibrin and polymorphonuclear leukocytic infiltration on the first one or two days. Organization then set in and an increasing amount of fibrous tissue was formed.

The following is the illustrative protocol for experiment 1 (fig. 1).

The experiment was started on April 7, 1931. The animal was an adult female shepherd dog, weighing 16.9 Kg. An autogenous kidney was transplanted. The time of the operation was from 9 to 11 a. m. The circulation to the transplanted kidney was restored in forty minutes.

Fig. 1.—Histologic appearance of an autogenous transplant of the kidney from day to day ($\times$ 130).

At the end of twenty-four hours the urinary excretion was profuse. Each cubic centimeter contained 1.080 mg. of urea and ammonia nitrogen (3.920 mg. from the normal kidney) and 0.384 mg. of creatinine (0.485 mg. from the normal kidney). The glomeruli were normal. There was a small amount of albuminoid material in a few capsular spaces. The epithelial cells lining many clusters of tubules were swollen, and their cytoplasm was granular, but their nuclei appeared

normal. Some of the tubules contained albuminoid material in their lumens. The interstitial tissue was normal. The capsule of the kidney revealed some extravasation and polymorphonuclear leukocytic infiltration.

At the end of forty-eight hours the urinary excretion was profuse. Each cubic centimeter contained 1.568 mg. of urea and ammonia nitrogen (1.950 mg. from the normal kidney), 0.259 mg. of creatinine (0.341 mg. from the normal kidney) and 1.650 mg. of sodium chloride (1.800 mg. from the normal kidney). The excretion of phenolsulphonphthalein during the first hour after the intravenous injection of 1 cc. of the dye was 7.4 per cent for the transplant as compared with 9.1 per cent for the normal kidney. The glomeruli were normal. Many of the tubules showed swelling and granular degeneration of the epithelial cells. Albuminoid material was present in the lumens of a few tubules. There was some congestion here and there in the interstitial tissue. The capsule of the kidney revealed extravasation, formation of fibrin, many polymorphonuclear leukocytes and a few fibroblasts.

At seventy-two hours the urinary excretion was good. Each cubic centimeter contained 1.850 mg. of urea and ammonia nitrogen (3.900 mg. from the normal kidney), 0.546 mg. of creatinine (0.526 mg. from the normal kidney) and 3.900 mg. of sodium chloride (2.370 mg. from the normal kidney). The glomeruli as well as the tubules were normal. The lumens of a few tubules contained albuminoid material. A few small areas of congestion were noted in the interstitial tissue. The capsule of the kidney showed extravasation, polymorphonuclear leukocytic infiltration, active proliferation of the fibroblasts and an increased amount of fibrous tissue.

At ninety-six hours the urinary excretion was scanty. Each cubic centimeter contained 0.714 mg. of urea and ammonia nitrogen (4.115 mg. from the normal kidney). The glomeruli were normal. The lumens of the tubules were dilated. The lumens of a few of the tubules contained albuminoid material. The interstitial tissue was normal. The capsule of the kidney showed extravasation, polymorphonuclear leukocytic infiltration, formation of new capillaries, active proliferation of the fibroblasts and an increased amount of fibrous tissue.

At the end of one hundred and twenty hours the urinary excretion was scanty. Each cubic centimeter contained 0.314 mg. of urea and ammonia nitrogen (2.272 mg. from the normal kidney). The glomeruli appeared somewhat smaller than usual. Marked granular degeneration of the epithelial cells was present in many of the tubules; in some there was cystic dilatation of the lumens, whereas a few other tubules contained albuminoid material. There were several small areas of congestion scattered throughout the interstitial tissue. The capsule of the kidney showed extravasation, formation of fibrin, polymorphonuclear leukocytic infiltration, active proliferation of the fibroblasts and an increased amount of fibrous tissue.

At the end of one hundred and forty-four hours the dog died of hemorrhage from a tear in the vein at the site of anastomosis. The transplanted kidney weighed 75 Gm., measured 7 by 4.5 by 4 cm. and showed a cloudy swelling. The normal kidney weighed 75 Gm. and measured 6.5 by 4 by 2.5 cm.

Functioning Homogenous Transplants: The glomeruli were normal. Albuminoid material was found in a few capsular spaces on the first two days in one of the experiments. The tubules usually appeared essentially normal for the first one or two days and then exhibited an increasing amount of swelling and granular degeneration or hyaliniza-

tion. On the other hand, the degenerative changes were observed on the first day, either to remain or to disappear later. Occasionally there was dilatation in the lumens of the tubules, which was evident either from the beginning or only toward the end of the experiment. With but one exception a varying number of tubules always contained albuminoid material. The interstitial tissue was normal on the first day. More commonly, however, a few collections of mononuclear cells and areas of congestion were present in the beginning, and they gradually increased in extent and intensity from day to day. Polymorphonuclear leukocytic infiltration, which occurred in several instances, was always found on the last day of the experiment. In one case the polymorphonuclear leukocytes were absent, and the necrosis seemed to be the consummation of a progressively increasing infiltration of mononuclear cells. The capsule of the kidney was the seat of extravasation, formation of fibrin and polymorphonuclear leukocytic infiltration until the second or third day, when organization and fibrosis began.

The illustrative protocol of experiment 11 (fig. 2) is as follows:

On October 12, 1931, a homogenous kidney was transplanted into an adult male shepherd dog weighing 14.8 Kg. The donor was an adult male shepherd dog weighing 10.3 Kg. The time was from 8:45 to 10:20 a. m. The circulation to the transplanted kidney was restored in twenty-five minutes. Immediately there was albuminoid material in a few capsular spaces and tubules. Otherwise the capsule of the kidney and the parenchyma were normal.

At the end of twenty-four hours the urinary excretion was profuse. Each cubic centimeter contained 2.284 mg. of urea and ammonia nitrogen (22.220 mg. from the recipient's kidneys), 0.162 mg. of creatinine (0.755 mg. from the recipient's kidneys) and 2.640 mg. of sodium chloride (1.485·mg. from the recipient's kidneys). The glomeruli and the tubules were normal. Albuminoid material was present in a few capsular spaces and tubules. There were numerous small areas of congestion, mononuclear cells and edema in the interstitial tissue. The capsule of the kidney showed extravasation, formation of fibrin, polymorphonuclear leukocytic infiltration and capillary proliferation.

At the end of forty-eight hours the urinary excretion was profuse. Each cubic centimeter contained 1.142 mg. of urea and ammonia nitrogen (26.667 mg. from the recipient's kidneys), 0.135 mg. of creatinine (1,250 mg. from the recipient's kidneys) and 4.455 mg. of sodium chloride (1.073 mg. from the recipient's kidneys). The glomeruli and the tubules were normal. Albuminoid material was present in a few capsular spaces and tubules. There were several collections of mononuclear cells, edema and diffuse congestion in the interstitial tissue. The capsule of the kidney showed extravasation, formation of fibrin, polymorphonuclear leukocytic infiltration, few newly formed capillaries and a proliferation of the fibroblasts.

At the end of seventy-two hours the urinary excretion was profuse. Each cubic centimeter contained 1.408 mg. of urea and ammonia nitrogen (24.990 mg. from the recipient's kidneys), 0.084 mg. of creatinine (0.760 mg. from the recipient's kidneys) and 4.538 mg. of sodium chloride (0.660 mg. from the recipient's kidneys). The glomeruli were normal. Granular degeneration of the epithelial cells was present in a number of tubules. The lumens of a few tubules were dilated. Albuminoid material was present in a few others. There were more and larger

collections of mononuclear cells and diffuse and marked congestion in the interstitial tissue. The capsule of the kidney showed extravasation, polymorphonuclear leukocytic infiltration, formation of new capillaries and active proliferation of the fibroblasts.

At the end of ninety-six hours the urinary excretion was scanty. Each cubic centimeter contained 1.428 mg. of urea and ammonia nitrogen (34.483 mg. from
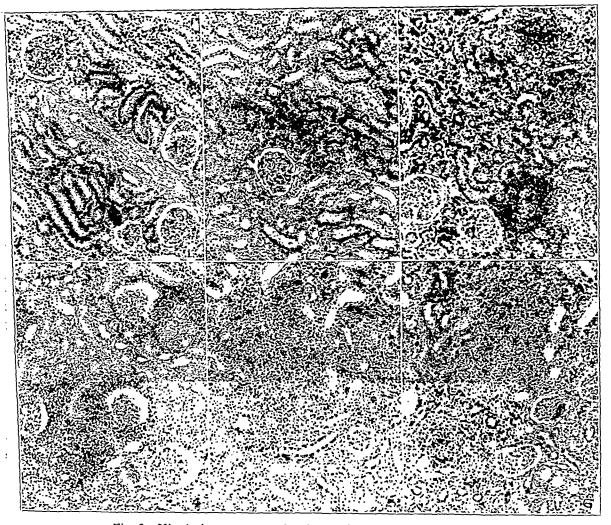
Fig. 2.—Histologic appearance of a functioning homogenous transplant of the kidney from day to day. The progressively more marked mononuclear cellular infiltration and the necrosis in the end may be noted ($\times$ 130).

the recipient's kidneys), 0.126 mg. of creatinine (1.379 mg. from the recipient's kidneys) and 6.436 mg. of sodium chloride (0.742 mg. from the recipient's kidneys). The glomeruli were normal. Many of the tubules were swollen, and there was granular degeneration of the epithelial cells. A few clusters of them were hyalinized. There was cystic dilatation of the lumens of a few

At the end of seventy-two hours the glomeruli appeared smaller than usual, and there seemed to be a relative thickening of the capillary walls. The tubules showed more swelling and granular degeneration and still contained an abundant amount of albuminoid material. There were a few small collections of mononuclear cells in addition to diffuse and marked congestion of the interstitial tissue. The capsule of the kidney showed more organization and fibrous thickening.

At the end of one hundred and twenty hours the glomeruli continued to appear smaller than usual. There seemed to be an increase in the number of cells, and the open capillary loops were not easily distinguishable. Most of the tubules were

Fig. 4.—Characteristic mononuclear cells that were found to invade the transplants (× 1,400).

destroyed. Albuminoid material was present in the few remaining tubules. There were congestion and polymorphonuclear leukocytic infiltration of the interstitial tissue, with many large areas of necrosis. The capsule of the kidney showed still more organization and fibrosis than before.

At the end of one hundred and forty-four hours an exploratory operation revealed thrombosis in the renal vessels. The transplanted kidney was necrotic.

Summary of the Histologic Data: Comparatively speaking, such changes as were observed to be present or absent in the glomeruli and tubules are not distinctive of either the autogenous or the homogenous kidney transplant. In both cases, the glomeruli showed no

particular structural alteration. Occasionally there was albuminoid material in a few capsular spaces. The tubules appeared normal or exhibited a varying amount of degeneration, or a change from one to the other. The degeneration of the epithelial cells, principally of those lining the convoluted tubules and the thick limbs of the loops of Henle, usually consisted of swelling and granular changes in the cytoplasm with the nuclei remaining apparently intact. Hyalinization of the cells also occurred.

Fig. 5.—Active proliferation of fibroblasts noted in the capsules of the transplanted kidneys (× 500).

In the autogenous and the homogenous transplants the collecting tubules and the thin limbs of Henle generally contained albuminoid material. But the amount seemed to be the most abundant in those homotransplants that failed to excrete urine. More or less dilatation of the lumens of a varying number of tubules also took place.

Mononuclear cells were found to invade both varieties of transplants (fig. 4). Instead of showing a diffuse distribution, they appeared in the perivascular region as often as in collections without special reference to any of the structural components of the kidney. In the auto-

transplant they seemed to occur in numbers somewhat proportional to the amount of degeneration. Sometimes they were altogether absent. In the homotransplant, on the other hand, there was usually a progressively increasing number of these cells. Often the degree of infiltration did not correspond to the amount of degeneration. The kidney even appeared otherwise normal. In the course of time mononuclear cells overwhelmed the transplant and destroyed it.

Necrosis occurred in one variety of transplanted kidney as well as the other. Most of the time, it was associated with a number of polymorphonuclear leukocytes. In a few instances in the homotransplantation series, however, only mononuclear cells were present.

The capsule of the kidney always revealed a varying amount of extravasation, formation of fibrin and polymorphonuclear leukocytic infiltration on the first one or two days after the autotransplantation or homotransplantation. Then organization began and progressed actively. The amount of fibrous tissue was markedly increased in a short time (fig. 5).

COMMENT

The operation of transplantation involves an unavoidable amount of exposure and manipulation of the organ and disturbance of its blood supply. The kidney is injured, as evidenced by structural degeneration and functional impairment. For the same reason, the biopsy operation is also harmful, although to a much less degree. But, remarkably enough, a kidney that is subjected to such a procedure every day often tends to resume a normal histologic appearance and to be improved functionally. However, this holds true only for the autogenous transplanted kidney. It seems that, under the unfavorable conditions which arise after transplanting the organ of one subject into the body of another the homogenous transplant possesses a diminished power of resistance to injury or fails to recover rapidly from it.

In the transplantation of tissues in general, a few lymphocytes may be found here and there in an autotransplant in the first few weeks. Soon the small collections of lymphocytes begin to disappear until they are no more than those present in normal tissue.[16] In a homotransplant, however, after seven or eight days a remarkable infiltration by lymphocytes takes place; these surround and invade the living tissue. In the case of renal tissue in particular, lymphocytes are only occasionally present in the autotransplant. In the homotransplant, however, they are found at first around and in the peripheral zone of the living renal tissue.[16] Then the lymphocytes collect about the tubules in increasing

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16. Loeb, Leo: Transplantation and Individuality, Physiol. Rev. **10**:547 (Oct.) 1930.

number and, after the tenth day, penetrate into the glomeruli and the lumens of the tubules.[17]

The mononuclear cells that have been found to invade the autogenous and homogenous transplants of the kidney are predominantly of the large mononuclear type and include relatively few lymphocytes. Probably the difference is one of terminology, and the same kind of cells are always involved in the reaction of the host to an autotransplant or a homotransplant.

It is to be expected that the cellular reaction should generally be evident as soon as the first or second day after transplanting the organ and rapidly increase in intensity. With an intact blood supply there is immediate and most intimate contact between the cells of the transplanted kidney and the fluids of the host.

Necrosis in areas of varying size was observed toward the end in several experiments. Usually it is associated with a large number of polymorphonuclear leukocytes. Sometimes only mononuclear cells are present. This may be the sequel of a mononuclear cellular infiltration, often extensive in the homotransplant, either directly or by interfering with the nourishment of the parenchyma. Then, as in the case of infarction, the invasion of the polymorphonuclear leukocytes is secondary to autolysis. But hydronephrosis and pyonephrosis are of frequent occurrence. A varying number of pus cells was invariably found in the urine. The urine was cultured twice, and both times the reaction was positive for Bacillus coli. Therefore, the pathologic picture probably represents pyelonephritis from an ascending infection of the urinary tract.

Thrombosis in the vessels at the site of anastomosis between the host and the transplant occurs more frequently after homotransplantation than after autotransplantation. However, this does not explain the peculiar functional behavior of the homogenous transplant of the kidney. Often when function has definitely failed, exploratory operations for several days afterward reveal the blood supply to be intact. Wounds in the kidney bleed profusely and heal well. Microscopic examination of specimens of the tissue removed at biopsy does not show thrombosis in the vessels or any sign of infarction. Instead of being the result of thrombosis, necrosis in the kidney often precedes it and seems to favor its occurrence.

The capsule of the kidney generally shows a marked increase in the amount of fibrous tissue. It probably exerts a constricting and injurious effect on the transplant by interfering with the blood supply and by preventing the change in the volume of the kidney which normally takes place.

17. Loeb, Leo: Further Investigations on Auto and Homoioplastic Transplantation of Kidney Tissue. J. M. Research **37**:229 (Nov.) 1917.

Although the difference in functional behavior between an autogenous and a homogenous transplant of the kidney may be explained to a certain extent on a pathologico-anatomic basis, the underlying cause for the existence of the pathologico-anatomic difference remains to be designated. In the absence of any definite knowledge, biologic factors are generally held responsible.

Loeb[16] suggested that after transplanting an organ from one animal into another of the same species, a homodifferential develops. In the inadequate environment it assumes injurious properties, either directly or after interaction with the body fluids of the host, being thus transformed into a homotoxin. And it is this toxin which calls into play the reactions on the part of the host. Neuhof[18] believed that tissue compatibility or incompatibility lies at the root of the problem. The basis is probably physicochemical.

The present state of knowledge points to two separate channels through which improvement in the results of homotransplantation may be expected.

The first possibility of improvement consists in the proper selection of the host and the donor. This is suggested by the experience of Dederer.[19] He used puppies of the same litter, and a transplanted kidney functioned well continuously until the host died from intercurrent distemper twenty-six days later. According to Loeb,[16] this falls into the category of syngenesiotransplantation rather than homotransplantation.

The second possibility lies in the suppression of individuality. The reactions against homotransplants are due to the active metabolism of the homogenous tissues or to the presence of very labile substances.[16] Siebert[20] has shown that it is possible, through graded exposure of the homogenous tissue previous to transplantation, to find an intensity of heat which, while allowing the tissue to live and to regenerate, does not to any extent attract the lymphocytes of the host. It is obvious, of course, that unless the function of the kidney is preserved, such a procedure is not applicable.

Surgery as a mechanical craft is almost complete. Operations have been performed on every organ of the body. Although it cannot be said that every operation has been conceived, it is clear that no startling innovation in the realm of pure surgical handicraft is to be expected, except possibly in the direction of the transplantation of organs.[21]

18. Neuhof, Harold: The Transplantation of Tissues, New York, D. Appleton and Company, 1923, p. 297.

19. Dederer, Carleton: Successful Experimental Homotransplantation of the Kidney and the Ovary, Surg., Gynec., & Obst. **31**:45 (July) 1920.

20. Siebert, W. J.: Effect of Graded Degrees of Heat upon Cartilage on Homoiotransplantation and Heterotransplantation in Guinea Pig, Proc. Soc. Exper. Biol. & Med. **26**:238 (Nov. 27) 1928.

21. Ogilvie, W. H.: Recent Advances in Surgery, ed. 2, London, J. & A. Churchill, 1929, p. 495.

Transplantation of the kidney gives promise of clinical usefulness. The destruction of both kidneys from tuberculosis, corrosive mercuric chloride poisoning or any other condition constitutes an indication for such a procedure. Under those conditions there is no other choice in order to prolong or to save the life of the person.

The experiments in autotransplantation have proved conclusively that the kidney can be transplanted. In clinical surgery, however, there is practically no occasion for autotransplantation. Heterotransplantation has been performed several times with complete failure as the uniform result.[22] Homotransplantation remains to be attempted. The difficulty, of course, lies in obtaining a human kidney transplant. But, it is not an insurmountable obstacle in view of the fact that a person can live normally with a single kidney.

The species of animals commonly used in the laboratory cannot be arranged in groups comparable to the blood groups of man.[23] In the experiments on homotransplantation, it is therefore not possible to select the donor on the basis of compatibility of the blood. Loeb[16] believed that it is improbable that the blood group of host and donor can be of great significance in this connection, while Neuhof thought that blood compatibility should be a basis for satisfactory results. It remains to be seen whether the clinical application of this principle will produce results different from and better than those obtained thus far in experiments on animals.

On the basis of our present knowledge of the subject there can be only one conclusion. As emphasized by Mann,[24] the successful transplantation of a healthy organ to replace a diseased one awaits the discovery of the biologic factors which prevent the survival of the tissue of one subject when transplanted into the body of another, together with the development of methods to hold the action of these factors in abeyance.

SUMMARY AND CONCLUSIONS

The purpose of this study is twofold: to ascertain the histologic changes which may take place in the transplanted kidneys from one day to another, and to note if there is a difference—qualitative, quan-

22. Jaboulay, M.: Greffe de reins au pli du coude par soudures arterielles et veineuses, Lyon méd. **107**:575, 1906. Ullmann, Emerich: Experimentelle Nierentransplantation, Wien. klin. Wchnschr. **15**:281 (March 13) 1902. Unger, Ernst: Nierentransplantationen, Berl. klin. Wchnschr. **47**:573 (March 28) 1910. Neuhof.[18]

23. Sanford, A. H., and Mann, F. C.: Unpublished data. Neuhof.[18]

24. Mann, F. C.: Transplantation of Organs, in Contributions to Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, The International Press, 1932. p. 757.

titative or in the sequence of events—between an autogenous and a homogenous transplant, as well as between a functioning and a nonfunctioning homotransplant.

Six autotransplantations and eighteen homotransplantations of the kidney were performed. Only five autotransplants and thirteen homotransplants were suitable for this study. Sixty biopsies were made. A total of one hundred and eighty histologic sections were examined.

Dogs were used for the experiments. The operations were performed under ether anesthesia and with sterile technic. The kidneys were transplanted by anastomosis of blood vessels into the neck. The functional capacity each day was estimated by the results of chemical analyses of the urine. The sequence of events in the histologic structures was followed by biopsies every twenty-four hours. The observations were limited to the first five days after transplantation.

All of the autogenous and six of the homogenous transplants functioned alike until the transplant was removed at operation, until the animal died or until thrombosis in one or both vessels or pyelonephritis occurred. One homotransplant excreted urine only part of the time, and six others failed to do so at any time during the period of observation. Thrombosis was not the cause of the failure to function, because in such cases exploratory operations revealed the vessels to be patent, and the biopsy wounds bled and healed as usual.

The autogenous and the homogenous transplants did not show distinctive changes in structure. In one as in the other, the glomeruli appeared normal, the tubules contained a varying amount of albuminoid material, dilatation or degeneration, and the capsule of the kidney had undergone organization and fibrosis. Quantitatively, however, in the case of the nonfunctioning homotransplants the tubules seemed to contain a greater amount of albuminoid material than usual.

Both varieties of transplants may show a few small collections of mononuclear cells on the first one or two days following transplantation. In the homotransplant, however, the infiltration is soon present in excess of the amount of degeneration and is followed by necrosis and destruction of the parenchyma. On the other hand, in the autotransplant, the number of those cells appears to be somewhat proportional to the severity and extent of the degenerative changes, and it tends either to remain the same or to diminish.

Although the course of changes that accrued from day to day was progressive in both cases, it seemed that in the autotransplant it was reparative, whereas in the homotransplant it was degenerative. No evidence was found to suggest the type of biologic factors which elicit the reaction between the host and the transplant after homotransplantation.

MEDIAL TORSION OF THE LEG

I. WILLIAM NACHLAS, M.D.

BALTIMORE

Although volumes have been written about the deformities of the leg, almost no clinical attention has been given to torsional deformities of the developmental type. If the observations reported here are correct, these deformities not only bear a genuine academic interest but are of considerable clinical importance. In fact, one must give recognition to these deformities if one is to explain certain phenomena associated with lateral bowing of the legs which cannot be properly explained by the mechanics of a lateral bend. The torsional abnormality is likewise needed to account for the failure of standard therapeutic procedures in the correction of well known deformities of the feet.

The studies were made on patients seen in the clinic for rickets of the Johns Hopkins pediatric service. The clinic material includes nonrachitic children with abnormalities of gait and posture, as well as those with the rachitic caricatures of physiologic curves, who supply excellent material for the investigation of deformities of developmental origin. As one observed these children, one frequently noted the waddling gait and the intoe so generally associated with bowlegs. But the amount of waddling and toeing in was by no means uniformly proportionate to the amount of lateral bowing. Furthermore, the mechanics associated with an outward bow did not fully explain the gait. The effort to clarify these discrepancies directed attention to the medial torsion of the leg, a term used to describe an inward twist of the lower part of the leg when the knees are kept in their normal position; that is, when the upper part of the tibia and fibula is held in the normal position, the lower part is rotated on the longitudinal axis so that the normal anterior surfaces are medially displaced. This deformity involves only the portion between the knee and the ankle and does not include the irregularities of the foot and thigh.

The recognition of torsional displacement of a cylindric body without adequate surface markings is difficult. For the same reason an inward twist of the leg can easily escape the eye of the clinician. The cylindroid shape of the leg and the paucity of obvious prominences and reliable landmarks, as well as the mobility of both ends, make it easy to overlook this type of deformity. The apparent criterion, the crest

of the tibia, cannot be accepted as reliable because normally it slants inward and becomes indeterminate in the lower half of the tibia. The asymmetrical placement of the lower malleoli with regard to the transverse axis of the ankle makes it all the more difficult to recognize the alinement of the ankle joint. It is easy to see, therefore, how a moderate torsional deformity can escape the eye of the examiner unless specific details for the recognition are supplied.

In the normal limb the knee faces directly forward as the foot, anatomically placed with regard to the ankle, points forward. This position becomes the clinical zero point from which medial twists may be measured in degrees as apparent torsion. The measurement of apparent torsion or clinical torsion must be differentiated from the absolute readings available to anatomists. In the dissected specimen it is
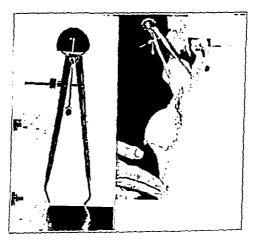
Fig. 1.—Torsionometer and method of use; the instrument consists of a caliper and pendulum with an indicator attached.

possible to measure the torsion of the leg accurately by projecting the transverse axis of the knee on the transverse axis of the ankle and reading the angulation. In fact, statistics are available that indicate that in the clinical normal there is an absolute average outward twist of 28.4 degrees.[1] It will be necessary, therefore, when the living patient is being considered to translate the absolute figures of the dissected leg into the apparent readings. Clinical readings may be made by supporting the foot in the normal right-angled relationship at the ankle, when the angle made by the foot with the anteroposterior axis of the knee can be estimated, or one may point the front of the knee directly upward and measure the torsion at the ankle with fair accuracy by the use of a simple caliper with a pendulum attached. More accurate measuring devices can be made, but they are cumbersome.

1. Strauss, William: Contrib. Embryol., 1927, vol. 19, no. 380.

Bearing these criteria in mind, one finds medial torsion present in persons of all ages. In adults it is seen only occasionally. In children attending the clinic for rickets it is by no means an infrequent sight, while in the nursery of the department of obstetrics it is found in about 80 per cent of the new-born. Prehistoric man, as represented by reconstructions of the Cro-Magnon, La Ferrassie and Spy men, and, more particularly, the anthropoid apes likewise show this characteristic.[1] If one studies the available measurements, translated into the clinically apparent figures, one finds that inward torsion exists in the adult
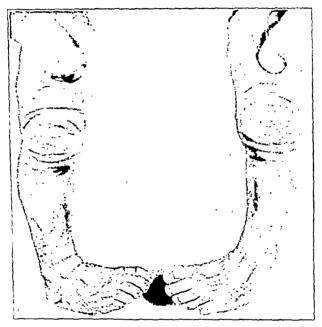
Fig. 2.—The amputated limbs of a new-born baby, demonstrating inward torsion of the legs.

orang-utan at 52 degrees; in the gorilla at 38 degrees; in prehistoric man at about 25 degrees; in the human 6 month fetus at 14 degrees; in the new-born at 17 degrees; in the juvenile at 11 degrees, and in the human adult at 0 degrees. From this one may deduce that our anthropologic ancestors began with an inward twist which has unwound itself phylogenetically and ontogenetically to produce the leg of the modern man. If this is true, one may consider atavistic reversion and developmental arrest etiologic factors for medial torsion. One might further expect that, as a rule, the unwinding process will have more opportunity to go on to its completion in the tall adult than in the person of stunted growth. Gross observations tend to substantiate this by revealing that

the inward twist is more prevalent in short people. It is likely that the unwinding takes place at the epiphyses rather than in the shaft, since (1) it acts during the period of growth, (2) it is evidenced in children who have for some reason or other never walked (this is a contradiction

Fig. 3.—A 2 year old rachitic child with torsion, showing outward facing of the patellas when the feet are in an approximately normal alinement.
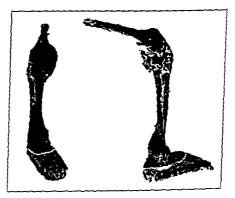
Fig. 4.—Legs dissected to show abnormal alinement of the tibia and fibula in medial torsion.

of Le Damany's assumption that it results from bipedal locomotion), and (3) it manifests itself in children whose bones have been kept hardened by intensive medication with viosterol. Bone-softening diseases such as rickets permit an exaggeration of the normal curves by inter-

ference with epiphyseal development and by allowing the shafts to bow under a superincumbent weight. As in the spine, extensive lateral bowing will generally be accompanied by rotation. This concomitance of rotatory deformity with lateral bend can be demonstrated in the laboratory if one attempts to angulate the softened bones of the leg laterally. Pathologic factors, such as infantile paralysis, distal malformations and traumas, are not considered in this paper. Sex variations are found to be negligible, and the predominance of colored patients over white is probably due to the greater incidence of rickets in the former.

<div align="center">PATHOLOGIC ANATOMY</div>

The normal adult tibia and fibula present the following important relations:

The fibula is lateral and posterior to the tibia in practically its entire length. The lower end of the fibula extends distal to the lower end of the tibial malleolus for a distance of approximately 1.5 cm. The transverse axis of the ankle cannot be established by the widest point between malleolar prominences. A more accurate gage, for clinical purposes, of the transverse axis of the ankle is one in which a line is drawn from the tip of the internal malleolus to the most prominent point on the anterior border of the lateral malleolus. The crest of the tibia does not supply a reliable landmark because in the lower half of the tibia it curves inward and loses its clearness. This fact is of importance because at first sight one might confuse the inward displacement of the crest with an inward twist of the leg. The fibula is normally articulated with the tibia at its proximal end with a true synovial membrane. There is a definite amount of mobility that can be obtained at this point in the dissected specimen. The lower tibiofibular articulation is much more firmly knit and does not present a clearcut synovial membrane. There is, nevertheless, an unmistakable amount of play available at this point. In the patient with inward torsion the fibula is carried forward by the tibial torsion so that the lower end of the fibula is not posterior, but anterior, to the bisecting frontal plane. Furthermore, a foreshortening of the fibula must take place, as it is spiraled around the tibia so that when the head of the fibula remains fixed the tip of the malleolus must be abnormally high. As a rule, in most of the patients with marked inward rotation the tip of the fibular malleolus is practically on a plane with the tip of the tibial malleolus.

<div align="center">CLINICAL PICTURE</div>

In the symptomatology and the physical findings one meets factors of considerable practical interest. The child is usually brought in with

the complaint of bowlegs. Occasionally the maternal complaint is that "the child walks pigeon-toed." Not infrequently a patient is referred because he is believed to have rickets, though he fails to show rachitic changes on clinical or roentgen examination. The primary picture is as follows:

1. It is noticed that an apparently healthy baby, possibly somewhat overweight but certainly quite active, walks with a marked inward pointing of the feet. If the child is allowed to stand, one finds no evidence of metatarsus varus or hallux varus. The foot is well balanced in its relation to the lower part of the leg. Frequently there is a pronounced lateral bow. If the patient is allowed to sit with the feet suspended over the edge of the table and the knees together, it is found that the feet point inward. This is particularly emphasized by the appearance of the extremity when the physician supports the foot with the ankle in the normal position. If the legs are stretched out on the table so that a line dropped through the prominence of the tibial tuberosity forms a perpendicular with the table, the lower part of the leg will be definitely twisted inward. While the aforementioned instrument proves of assistance in recording the amount of twist, it is not necessary for gross recognition of the deformity. It is noteworthy that the abnormal gait is much more pronounced when the patient is actually walking than when he is standing still.

2. Again, many patients present themselves because of bowlegs. When the patient is allowed to lie on the table and the feet are apposed, however, no gross lateral bowing is observed. This observation was particularly brought forth during the recently prevailing fashion for knee-length skirts. Young women seeking assistance for what appeared to them cosmetic deficiency not infrequently failed to find sympathy in the attending physician because of this apparent lack of separation between the inner aspects of the limbs when the feet were apposed. On the other hand, in patients of this type one finds that the alinement of the feet has been accomplished by the relative external rotation of the limbs at the hips, with the result that the normal posterior fulness of the calf is displaced toward the midline so as to obscure the distance between the inner borders of the leg. The patient, however, is fully aware of the distortion, because when she assumes her normal gait the deformity becomes apparent. In patients of this sort, if the examining physician looks for the patellas when the feet are held together, he finds that they are facing distinctly outward. In an attempt to correct the awkward toeing in, the patient may of his own accord follow one (or both) of two courses: (1) eversion of the entire limb at the hip or (2) abduction of the foot at the mediotarsal joint.

3. The first of these compensatory maneuvers is responsible for another clinical manifestation, the bow-legged waddle. The gait is characteristic. There is a swaying of the trunk from the midline as each step is taken. It is not a shuffle such as one finds in the child with knock knee. At each step the trunk is swung onto the sustaining limb. The gait is not unlike that seen in patients with paresis of the gluteus medius and minimus muscles. Utilizing this comparison, one finds that the child who externally rotates the entire leg to compensate for the inward pointing of the foot impairs the function of the lesser glutei. The effect of the movement is to approximate the origin and insertion of the abductors of the leg, that is, the gluteus medius and minimus muscles. This results in a diminished function of the muscles so that assistance must be given to them by tilting the trunk to bring the center of gravity more nearly over the femoral head. Examinations of articulated skeletons as well as of normal adults indicate that an external rotation of 40 degrees shortens the distance between the greater trochanter and the approximate center of action of the gluteus medius and minimus muscles by from 1.5 to 2 cm., or by approximately 10 per cent of the normal distance. Care must be taken to rule out coxa vara.

4. The second compensatory maneuver, abduction of the foot at the mediotarsal joint so that the front part of the foot bears the normal walking alinement while the posterior portion retains the inward twist, gives one the fourth clinical anomaly. This abduction produces talipes valgus and the patient appears for treatment for flatfoot. It is not uncommon to find that children who stand with abduction of the foot walk with a marked varus gait, the so-called paradoxical clubfoot. The explanation for this paradox on the basis of the strain-relieving muscular pull when the child is walking is inadequate for all cases. Many of the children walk with an exaggerated toeing in, in spite of a mechanical support supplied to relieve the foot strain. On the other hand, the inward twist of the leg affords an explanation for the pigeon-toe gait in the presence of static valgus.

ROENTGENOGRAPHIC OBSERVATIONS

Most of the studies to which the patients were submitted required roentgenograms. It was natural, therefore, that one should expect reports of torsional deformities from the roentgenographic department. Since reports of this type were not forthcoming, an attempt was made to determine some roentgenologic corroboration of the clinical impressions. Unless one looks for certain specific factors, one may easily pass by many of the roentgenograms as showing no abnormalities.

To establish differential factors, roentgenograms were taken of a normal tibia and fibula. It was found that under the standard methods of exposure the shadow of the entire fibula lay beside the shadow of the tibia without overlapping. This was noted on both anteroposterior and lateral views. If, then, the bones were softened and an experimental torsion of 30, 60 or 90 degrees was made in the bones of the leg, the roentgenograms demonstrated an overlapping of the distal portions of the bones when the proximal portions were held in their normal relationship. A check-up between the clinical notes and the roentgen readings on my patients showed definite qualitative and quantitative
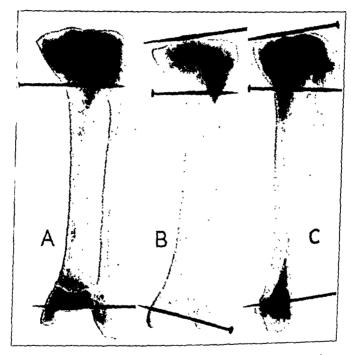
Fig. 5.—Roentgenogram of the decalcified bones of the leg showing: *A*, normal roentgen alinement of the tibia and fibula; *B*, experimental torsion of 30 degrees, when the fibular head overlaps the tibial head while the malleoli are in normal relationship, and *C*, experimental torsion of 90 degrees with the heads of the bone in a conventional roentgen position showing overlapping of the lower portions of the bones.

conformity. The amount of overlapping of the distal portions of the bones can be used to determine approximately the degree of deformity. Thus, if the shadow of the fibular malleolus covers half of the tibial expansion, a deformity of 45 degrees may be expected.

DIFFERENTIAL DIAGNOSIS

From the foregoing comment it must be apparent that in the differential diagnosis one must be careful not to confuse the condition with

hallux varus, metatarsus varus, traumatic torsional displacement and congenital dislocation of the hip. Coxa vara may produce a waddle, but it will usually have an associated restriction of abduction. Care should be taken not to confuse the inward swing of the crest of the tibia with true rotational distortion of the leg.

Fig. 6.—Roentgenogram of a leg with medial torsion of 45 degrees, showing superimposition of malleolar shadows when the upper ends are conventionally placed.

TREATMENT

The therapeutic measures involved are rather obvious. External rotatory maneuvers are desirable, but should be limited to the leg proper. Repeated manipulations at frequent intervals to unwind the bones of the leg are thus of considerable assistance in early childhood. The bowleg brace described by Bradford and Lovett, which allows control of rotation of the limb through an extension above the hip, is valuable in somewhat older patients. The osteotomies, particularly those described

by Peabody,[2] will be found necessary in adults and older children. It must be emphasized that the elevation of the inner border of the heel and sole in the child with flatfoot resulting from inward twisting, while beneficial to the alinement of the foot, is not likely to assist in the recovery of the torsional deformity. Any corrective measure which changes the weight-bearing surface of the shoes involves the undesirable factor of loss of efficiency through the rather mobile ankle joint. As in the therapeusis of ordinary bowleg, the earlier treatment is begun, the more easily correction of the deformity is accomplished.
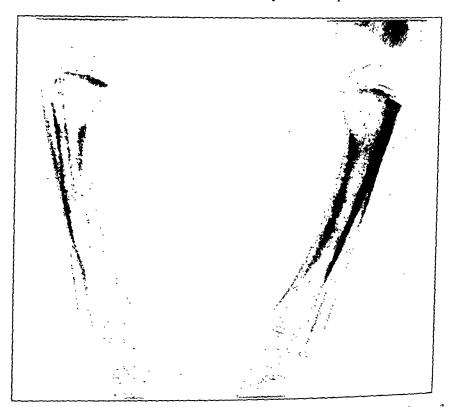
Fig. 7.—Anteroposterior roentgenogram of the legs of the child in figure 3. The overlapping shadows of the heads of the bones is to be noted, though the lower ends are in the usual alinement.

SUMMARY

1. Attention is called to the existence of medial torsion of the leg of sufficient degree to be of clinical importance.

2. The deformity is not necessarily rachitic in origin. Evidence is presented to indicate that it is of developmental origin, and that it persists because of a developmental arrest, possibly exaggerated by postnatal factors.

2. Peabody, C. W.: J. Bone & Joint Surg. **14**:822 (Oct.) 1932.

3. Of the clinical manifestations, the more important are the toeing in and the waddling gait. The mechanics of this deformity afford a rational explanation for these symptoms.

4. It is possible to recognize the deformity by the roentgenographic criteria enumerated, but measurement of the clinical torsion is best made by the simple instrument described.

5. It is important to direct treatment to the leg rather than to the foot.

SYMPATHETIC GANGLIONS REMOVED SURGICALLY

A HISTOPATHOLOGIC STUDY

ALBERT KUNTZ, Ph.D., M.D.

ST. LOUIS

The results of sympathetic ganglionectomy in the surgical treatment of disease in many cases strongly suggest that dysfunction of the autonomic nerves is a factor in the disease process in question. The basic causes of the autonomic dysfunction, however, are not as yet fully understood. Lesions of the autonomic ganglions and ganglion cells doubtless must be regarded as important factors in many cases, but our knowledge of these lesions and their functional significance is fragmentary and incomplete.

REVIEW OF THE LITERATURE

Most of the data available at present regarding lesions of the autonomic ganglions and ganglion cells represent the results of histopathologic studies of preparations of ganglions obtained at autopsy following death due to a wide variety of causes. The earlier studies of this character, the results of which have been published, have been reviewed by Stämmler [1] (1923), who also reported the results of his own studies of ganglions obtained at autopsy in a large series of cases. On the basis of this review and the results of his own studies, Stämmler concluded that infectious disease usually is accompanied by pathologic changes in the autonomic ganglions and in many of the ganglion cells. In cases of acute infectious disease, the autonomic ganglions commonly become hyperemic and infiltrated with wandering cells, and the ganglion cells undergo degeneration in a greater or lesser degree. The infiltrating cells are mainly lymphocytes and mononuclear leukocytes which appear in large numbers in the perivascular lymphatics, but also invade the connective tissue and, in many instances, the ganglion cell capsules. The earliest recognizable changes in the ganglion cells, according to Stämmler, consist in enlargement of the nucleus and an apparent reduction in the quantity of intranuclear chromatin. The nuclear membrane also becomes thinner and less distinct, and the nucleolus may disappear. If the nucleus remains intact, it may maintain its normal position in the

cell or become displaced into an eccentric position. Later, it may undergo reduction in size and become pyknotic. In the latter condition, it also exhibits a more intense staining reaction than does the normal nucleus. The earliest reaction of the cytoplasm involves swelling and a reduction in the intensity of its staining reaction. With the reduction in the size of the nucleus, the cytoplasm also undergoes a reduction in volume. In many ganglion cells, the initial changes are followed by atrophy leading to necrosis.

In cases of chronic infectious disease and other chronic pathologic states, particularly in older persons, as observed by most of the earlier investigators, the autonomic ganglions also exhibit a marked increase in the interstitial connective tissue. The chromidial content of many of the ganglion cells is diminished, and many of them contain melanotic pigment. The capsules of some of the ganglion cells also become thickened, and the capsule cells undergo proliferation.

The results of Mogilnitzky's [2] (1923, 1924 and 1927) studies on the histopathologic changes in the autonomic ganglions in cases of infectious disease in general corroborate those of Stämmler. Both of the investigators pointed out that the lesions observed in the autonomic ganglions are nonspecific and probably bear no direct relationship to the etiology of the disease in question.

The studies based on preparations of sympathetic ganglions removed surgically in the treatment of disease, the results of which have been published, also failed to reveal lesions in the ganglions or ganglion cells which could be regarded as directly related to the disease in question. In preparations of the cervical sympathetic ganglions removed by operation in a limited series of cases of Raynaud's disease and angina pectoris, Stämmler [3] (1924) described changes comparable to those observed in preparations of the autonomic ganglions in cases of chronic infectious disease. Clark [4] (1927) also observed no histopathologic changes which could be correlated with angina pectoris in preparations of the superior cervical sympathetic ganglions removed by operation in seven cases of the disease. Craig and Kernohan [5] (1933), who recently reported their

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2. Mogilnitzky, B.: Die Veränderungen der sympathischen Ganglien bei Infektionskrankheiten, Virchows Arch. f. path. Anat. **241**:298, 1923: Die pathologische Anatomie des vegetativen Nervensystems beim Recurrens, ibid. **248**:137, 1924; Die pathologische Anatomie des vegetativen Nervensystems bei Malaria, ibid. **263**:839, 1927.

3. Stämmler, M.: Anatomische Befunde am sympathischen Nervensystem; Vasomotorische Neurosen, Deutsche med. Wchnschr. **50**:457, 1924.

4. Clark, S. L.: The Superior Cervical Sympathetic Ganglion in Angina Pectoris; a Microscopic Study, J. Lab. & Clin. Med. **13**:101, 1927.

5. Craig, W. McK., and Kernohan, J. W.: The Surgical Removal and Histologic Studies of Sympathetic Ganglia in Raynaud's Disease, Thrombo-Angiitis Obliterans, Chronic Infectious Arthritis, and Scleroderma, Surg., Gynec. & Obst. **56**:767, 1933.

findings in preparations of the sympathetic ganglions removed by operation in an extensive series of cases, including Raynaud's disease, thrombo-angiitis obliterans, chronic infectious arthritis and scleroderma, observed no significant histologic differences between the ganglions removed from patients with the various diseases and expressed the opinion that the changes present do not deviate beyond the normal limits, and that most of them can be explained on the basis of advancing age.

MATERIAL AND METHODS

The present study is based on preparations of sympathetic ganglions removed surgically from thirty patients, including nineteen with chronic polyarthritis, two with Raynaud's disease, two with thrombo-angiitis obliterans, one with endarteritis, one with spastic hemiplegia, one with progressive muscular dystrophy, one with adenothyrotoxicosis, one with pruritus ani and pruritus vulvi and one with congenital megacolon. The patient with congenital megacolon was 6, the one with spastic hemiplegia, 7, and the one with progressive muscular dystrophy, 11 years of age. The others ranged from 18 to 69. Of these, twenty-two were patients of Dr. W. T. Coughlin and eight, patients of Dr. J. F. Clancy, to both of whom I am indebted for the ganglions removed and the essential data contained in the cases reported here.

All of the ganglions were fixed in formaldehyde. Most of the preparations used were stained with toluidine blue and erythrosin; the rest, with cresyl violet. In addition to the preparations of the ganglions removed in the surgical treatment of disease, preparations of human sympathetic ganglions obtained at autopsy and sympathetic ganglions obtained from normal animals were available for comparative study.

As has been pointed out in the review of the literature, most of the earlier investigators who studied human autonomic ganglions obtained at autopsy, regardless of the causes of death, in a great majority of the cases observed histologic changes in the ganglions which they regarded as pathologic in slight degree. Our own studies of preparations of human autonomic ganglions obtained at autopsy following death due to a wide variety of causes in nearly every instance revealed conditions which, in comparison with the conditions observed in preparations of the ganglions of laboratory animals, cannot be regarded as normal. It has not been regarded as advantageous, therefore, to attempt to establish a norm, on the basis of human material, with which to compare the findings in the preparations of the sympathetic ganglion removed by operation. For the purposes of the present study, the autonomic ganglions of vigorous laboratory animals (cats) have been regarded as more nearly normal than the available human material obtained at autopsy.

HISTOPATHOLOGIC OBSERVATIONS

In the series under discussion, the preparations of sympathetic ganglions removed surgically, as compared with preparations of the ganglions of normal animals, with few exceptions, probably deviated from the range of normal variation in certain particulars. In most cases, they exhibited changes which have not been observed in preparations of the ganglions of normal animals. These changes varied in intensity within relatively wide limits in different individuals, but belonged to the same categories; consequently, they could not be regarded as specific for the disease in question in any case.

Preparations of all of the ganglions removed surgically in the series exhibited infiltration in some degree of the interstitial connective tissue with wandering cells, mainly lymphocytes and mononuclear leukocytes. The preparations of some of the ganglions, particularly those of the older patients, also exhibited hyperplasia of the interstitial connective tissue. The wandering cells present in the interstitial connective tissue stood out prominently in preparations of the ganglions by reason of the intense staining reaction of their nuclei (fig. 1 *B* and *C*). In the preparations of some of the ganglions the cells were present in small numbers and occurred either in groups or widely scattered in the interstitial tissue. In those of other ganglions lymphocytes and mononuclear leukocytes were present in larger numbers throughout the interstitial tissue. In four cases, they were observed to be particularly abundant around some of the smaller blood vessels (fig. 2), where many of them lay within the perivascular lymphatics.

In many instances cells apparently identical with the wandering cells in the interstitial tissue were present within the ganglion cell capsules. Some of these
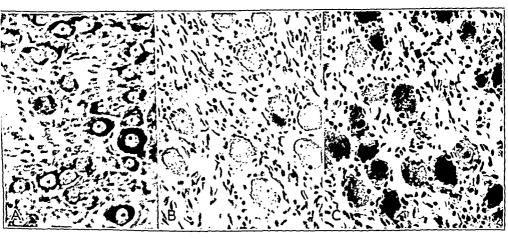
Fig. 1.—*A*, photomicrograph of a section of the sympathetic ganglion of a normal animal (cat) ; *B*, photomicrograph of a section of the cervical sympathetic ganglion removed surgically from a patient, 11 years of age, with progressive muscular dystrophy, showing infiltration with wandering cells; *C*, photomicrograph of a section of the lumbar sympathetic ganglion removed surgically from a patient with chronic polyarthritis, showing hyperplasia of the interstitial connective tissue and infiltration with wandering cells.

probably were wandering cells which had invaded the capsules; others probably arose owing to the proliferation of capsule cells. Some of the preparations also afforded evidence of proliferation of reticulo-endothelial cells in areas adjacent to the ganglion cell capsules.

In the interstitial tissue the relatively large caliber of many of the capillaries and small veins, partially or completely filled with blood cells, suggested hyperemia of the ganglions. This condition was possibly due in part to manipulation of the ganglion during the operative procedure. The fact, however, that sympathetic ganglions which were removed at autopsy and which exhibited evidence of chronic inflammation also were hyperemic favored the assumption that the hyperemia apparent in the ganglions in our series was related to other changes

in the ganglions. Not infrequently, aggregates of polymorphonuclear leukocytes appeared in contact with the endothelium of the vessels containing blood cells. In some of the cases, eosinophils made up a relatively high percentage of the cells.

In approximately one third of the cases some of the small arteries and veins in the ganglions exhibited marked thickening of the walls (fig. 3). The thickening

Fig. 2.—Photomicrographs of sections of the sympathetic ganglions removed surgically from patients with chronic polyarthritis, showing aggregations of wandering cells around small blood vessels.

Fig. 3.—Photomicrographs of sections of sympathetic ganglions removed surgically from patients with chronic polyarthritis, showing thickening of the walls of the small arteries.

was brought about in part by hyperplasia of the cellular elements, but in a larger measure by hypertrophy of the fibrous elements. In some of the ganglions, many of the smaller vessels, particularly small arteries and arterioles, also exhibited proliferation of the endothelium lining the intima. In some instances, invading white cells also were present in the vessel walls.

The changes in the ganglion cells included swelling and shrinking of the nucleus and cytoplasm, increase and diminution in the chromatin content of the nucleus and in the chromidial substance in the cytoplasm, pigmentation, vacuolation, hyaline degeneration and destruction by phagocytes.

Nearly all of the preparations in the present series contained some ganglion cells which were definitely swollen (fig. 4). The cells were in some instances enlarged to two or three times their normal size. They were present in only small numbers, except in the more pathologic ganglions. For example, the preparations of the ganglions of one of the patients with polyarthritis (arthritis deformans) exhibited swollen ganglion cells in large numbers. The preparations also exhibited numerous shrunken hyperchromatic ganglion cells as well as ganglion cells which had undergone no marked changes in volume but which contained a relatively meager supply of chromidial substance. The swelling and the shrunken hyperchromatic condition of the ganglion cells in this case were obviously not directly related to the arthritis, but were probably related to other pathologic processes, of which the record of this case affords evidence. In some of the swollen cells, the nucleus appeared abnormally large and vesicular and reacted
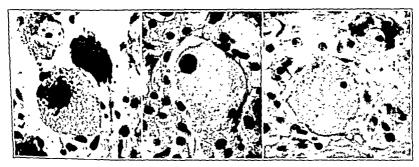
Fig. 4.—Photomicrographs of sections of sympathetic ganglions removed surgically from patients more than 50 years of age with chronic polyarthritis, showing swollen ganglion cells.

but lightly to the stain. In others, the nucleus was somewhat shrunken, slightly irregular in outline and reacted more or less intensely to the acid stain. The cytoplasmic body was so large that it completely filled the cell capsule, causing the latter to be considerably distended and reduced in thickness. Some of these swollen ganglion cells exhibited a narrow perinuclear zone in which there remained some chromidial substance, while the peripheral zone was devoid of this substance. Others exhibited only traces of chromidial substance in the cytoplasm. In the latter cells, the cytoplasm appeared finely granular and almost colorless.

The preparations of all the ganglions in the series exhibited some ganglion cells which were definitely shrunken and hyperchromatic. This condition was illustrated by the more intensely stained ganglion cells in figs. 1 *C* and 2 *B*. The chromidial substance in the cytoplasm, although abundant, did not appear in discrete chromidial bodies but in fine granules or in solution. In erythrosin-toluidine blue preparations, the cytoplasm assumed a diffuse blue or reddish color, depending on the degree of change which had taken place. The nuclei of many of the ganglion cells in this condition reacted intensely to the acid stain; those of others exhibited an excess of chromatin. Ganglion cells in this condition were present in relatively small numbers in the preparations of most of the ganglions.

Preparations of the ganglions of several patients, however, exhibited shrunken hyperchromatic ganglion cells in relatively large numbers. Of these, one was a patient, aged 11 years, with progressive muscular dystrophy; another, a patient 46 years of age, with paralysis agitans; another, the patient with arthritis deformans referred to earlier. The last patient was 52 years of age. The preparations of the ganglions of this last patient also exhibited numerous swollen ganglion cells.

Preparations of all the ganglions in the present series also exhibited some ganglion cells in which a portion of the cytoplasmic body was completely or almost completely devoid of chromidial substance and showed evidence of hyaline degeneration. In most of the cells, the nucleus was situated in an eccentric position at the periphery of the hyaline area. In most of the preparations, ganglion cells in this condition were present in only small numbers. In others, particularly those in which shrunken hyperchromatic ganglion cells were numerous, they were present in considerable abundance. These preparations also exhibited ganglion cells which probably represented intermediate stages between the shrunken hyperchromatic cells and those which showed frank hyaline degeneration. Ganglion cells which seemed to be undergoing hyaline degeneration were particularly abundant in the preparations of the ganglions of the patient with endarteritis. This patient was 44 years of age and gave a history of alcoholism and addiction to drugs.

One of the most uniform deviations from the condition of the majority of the ganglion cells in preparations of the ganglions of normal animals observed in the series of preparations was a reduction in the size of the chromidial bodies and in the quantity of the chromidial substances in the cytoplasm. In most of the ganglions used in this study, the chromidial substance was relatively meager in the great majority of the ganglion cells. The chromidial substance present in these cells existed in minute granules or in the form of chromidial dust. In the cells in which the chromidial substance was present in greater abundance, it commonly existed in the form of discrete chromidial bodies similar to those present in the ganglion cells of normal animals. The chromidial substance may be distributed more or less uniformly throughout the cytoplasm, or it may be concentrated mainly in either the perinuclear or the peripheral zone. The latter condition was most common in our preparations. Most of the ganglion cells which contained little chromidial substance in the cytoplasm also exhibited some diminution in the size of the nucleus and in the quantity of intranuclear chromatin.

Accumulations of pigment granules in the cytoplasm of many of the ganglion cells could be observed in the preparations of all the ganglions in the series, except those of the two youngest patients, who were 6 and 7 years of age, respectively. In some of the ganglions, relatively few ganglion cells were pigmented, and most of these only slightly. In others, pigment was present in nearly all of the ganglion cells, many of them being heavily pigmented. The pigment existed in dark granules of unequal size. In some cells, the pigment granules were scattered in small aggregates throughout the cytoplasm (fig. 5 *A* and *B*); in others, they constituted heavy, dark masses near the periphery of the cell body (fig. 5 *C*).

As previously stated, cells which probably were phagocytic were present within the capsules of some of the ganglion cells. In some of the ganglions, these cells were present in only a few of the ganglion cell capsules and only in small numbers; in others, they were present within the capsules of many of the ganglion cells. In many instances, the ganglion cell capsules were markedly thickened and the numbers of cells lining them were increased.
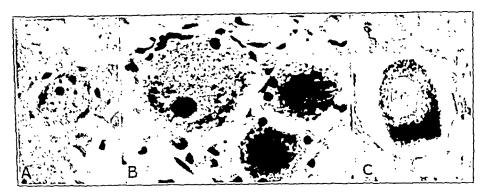
Fig. 5.—Photomicrographs of sections of sympathetic ganglions removed surgically, showing pigmented ganglion cells. In *A* and *B*, the pigment granules are in small aggregates throughout the cytoplasm; in *C*, they constitute heavy, dark masses near the periphery of the cell body.
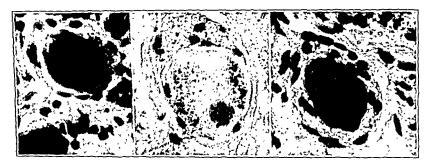
Fig. 6.—Photomicrographs of sections of sympathetic ganglions removed surgically, showing thickening of the ganglion cell capsules.

Fig. 7.—Photomicrographs of sections of sympathetic ganglions removed surgically, showing advanced neuronophagia.

The thickening of the capsule involved mainly its noncellular membranous portion in contact with which the endothelial cells lining the capsule rested (fig. 6). The latter cells normally constituted a single layer. In some of the thickened capsules, the endothelial cells had increased in number, and some of them no longer lay in direct contact with the membranous layer of the capsule. Some of the cells within the capsules probably represented endothelial elements which had become separated from the lining of the capsule; others, doubtless, had invaded the capsules from the interstitial tissue. The cells within a capsule gradually encroached on the ganglion cell and apparently consumed its cytoplasm (fig. 7). This phenomenon could be observed in nearly all of the preparations in the series but was most apparent in those of the ganglions of the older patients. In these ganglions, free cells were present within the capsules of a relatively large percentage of the ganglion cells. Most of the ganglion cells showed little destruction of cytoplasm; others exhibited consumption of the major portion of it. Ganglion cells in the latter condition also appeared necrotic.

<div align="center">COMMENT</div>

The histopathologic changes in the sympathetic ganglions and ganglion cells already described fall into the same general categories as those described by earlier investigators, particularly Stämmler (1923 and 1924) and Mogilnitzky (1923 to 1927), in material obtained at autopsy in cases of infectious disease and in ganglions removed surgically in cases of Raynaud's disease and angina pectoris. The observations of Craig and Kernohan (1933) in the most extensive series of sympathetic ganglions removed surgically which has been available for study also fall into these categories, but these investigators regarded the changes observed as within the limits of normal variation. In comparing their observations with those of the earlier investigators already named and those set forth in this paper, it is significant to note that the criterion of the normal histologic structure of sympathetic ganglions used by them is based on a study of sympathetic ganglions obtained at autopsy in forty consecutive cases following death due to various causes. Although none of these patients had suffered from any of the conditions for which ganglionectomy had been done in their surgical series, no cognizance seems to have been taken of possible histopathologic changes in the ganglions which might be correlated with other pathologic processes. A norm established in this manner obviously represents a much wider range of variation than one based on a study of the ganglions of normal animals.

The histologic changes in many of my preparations conformed closely to those described by Craig and Kernohan. The preparations of some of the ganglions in the series, however, exhibited changes which seem to be more marked than were the corresponding changes described by these two investigators. For example, the interstitial connective tissue was so abundant in some of the ganglions that I could not avoid

the conclusion that hyperplasia of this tissue had taken place. Wandering cells also were present in greater abundance throughout the interstitial tissue in some of the ganglions in my series than was indicated by the account of Craig and Kernohan. In the ganglions of four patients in the series, as already stated, these cells were particularly abundant around small blood vessels. Like some of the earlier investigators, particularly Stämmler (1923), I regarded these phenomena as indicative of chronic inflammation of the ganglions in which they were present.

Some of my preparations also exhibited more extensive destruction of ganglion cells in the presence of free cells within the ganglion cell capsules than is indicated by the account of Craig and Kernohan. Although they observed indentations in ganglion cells in the presence of free cells within the capsules, they did not regard this as indicative of phagocytosis, since débris having an affinity for silver could not be demonstrated in the intracapsular cells. In view of the extensive destruction of ganglion cells, in the presence of free intracapsular elements, which I observed in some of my preparations, I assumed that some at least of the free cells within the ganglion cell capsules were phagocytes. This also was in agreement with the interpretation of Spiegel and Adolf [6] (1922), who reported extensive destruction of sympathetic ganglion cells by the phagocytic action of free cells within the ganglion cell capsules. According to their observations, neuronophagia may be brought about both by phagocytes which invade the ganglion cell capsules and by cells derived from the endothelium lining the capsules.

The functional significance of the changes in the sympathetic ganglions and ganglion cells described is as yet not fully known. That changes in the volume ratios of the nucleus and the cytoplasm of nerve cells and changes in the quantity of chromidial substance in their cytoplasm are correlated with cell activity, however, has been demonstrated experimentally. In an extensive study of the cytologic changes brought about in the Purkinje cells in the cerebellum, in experimental animals subjected to continued stimulation, Dolley [7] (1911) described an orderly sequence of change involving the nucleus-plasma ratio and the chromidial substance. The initial response of these cells to stimulation, according to Dolley, was an increase in size and increased production of chromidial substance, so that the cells became hyperchromatic. Following this phase, the cells began to shrink and the hyperchromatism receded, but the nuclei showed evidence of edema, and the nucleus-plasma ratio was shifted in favor of the nucleus. As the chromidial

6. Spiegel, E. A., and Adolf, M.: Die Ganglien des Grenzstranges, Arb. a. d. neurol. Inst. a. d. Wien Univ. **23**:67, 1922.

7. Dolley, D. H.: Studies on the Recuperation of Nerve Cells After Functional Activity from Youth to Senility, J. M. Research **24**:309, 1911.

substance was diminished beyond the normal level for the resting cell, secondary restoration of this substance set in. At first it was piled up about the nuclear membrane and then displaced toward the periphery. Following this phase, diminution of the chromidial substance again set in and continued until little chromidial substance or none remained apparent in the cytoplasm. The nucleus also appeared to be almost entirely devoid of chromatin. During this phase, the nucleus shrank, and the nucleus-plasma ratio was shifted in favor of the cytoplasm.

Studies of the effects of stimulation on the autonomic ganglion cells comparable to those of Dolley on the effects of stimulation of the Purkinje cells were not available. Some significant data bearing on the effects of stimulation on the ganglion cells of the celiac plexus, however, were at hand. A sequence of change in the chromidial substance and the nucleus-plasma ratio in these cells in the albino rat, which, in the main, paralleled that described by Dolley in the Purkinje cells, particularly in the dog, was described by Bradshaw [8] (1930) following exposure of the animals to roentgen rays and by Ingersoll [9] (1934) following stimulation of the abdominal viscera.

On the basis of studies of preparations of the celiac ganglions of normal rats at rest, both Bradshaw and Ingersoll classified the ganglion cells in three groups according to the quantity and distribution of the chromidial substance in the cytoplasm and the nucleus-plasma ratio. The cells of group I possess an abundant supply of chromidial substance which is distributed more or less uniformly throughout the cytoplasm. The great majority of the ganglion cells in the preparations of the ganglions of normal rats fall into this group. The cells of group II are, on the average, somewhat smaller than those of group I and possess less chromidial substance, which usually is distributed mainly in the perinuclear or the peripheral zone. Only a small percentage of the ganglion cells fall into this group. The cells of group III are, on the average, somewhat smaller than those of group II and possess still less chromidial substance. Some are almost devoid of this substance and exhibit only a little chromatin in the nucleus. This group is represented by only a few cells in the ganglions of the normal resting animals. By differential counting of the cells in the several groups in preparations of the celiac ganglions from normal resting animals and from animals which had been subjected to the means of stimulation already named, both Bradshaw and Ingersoll were able to demonstrate a progressive decrease in the percentage of the ganglion cells in group I and an increase in the percentage of those in groups II and III as the duration or the intensity of the stimulation was increased.

8. Bradshaw, V.: Unpublished thesis, 1930.

9. Ingersoll, E. H.: The Effect of Stimulation upon the Coeliac Ganglion Cells of the Albino Rat, J. Comp. Neurol. **59**:267 (April) 1934.

According to Ingersoll, the initial response of the celiac ganglion cells to stimulation seems to be the increased production of chromidial substance, which results in hyperchromatism and slight enlargement of the cells. After this, the chromidial substance is diminished until it approaches the normal level and the cell undergoes some reduction in size, with a shifting of the nucleus-plasma ratio in favor of the nucleus. If stimulation is continued, the chromidial substance undergoes further diminution until the cytoplasm is practically devoid of this substance. Having given up most of its chromatin, the nucleus also appears pale and vesicular. These observations support the assumption that chromidial substance is produced and consumed during the activity of the ganglion cells. During the early phases of activity, its production exceeds its consumption and the result is hyperchromatism. During the later phases, chromidial substance is consumed more rapidly than it is produced and its supply gradually becomes depleted.

In view of these experimental data, which indicate that prolonged ganglion cell activity results in diminution in the amount of chromidial substance in these cells, the assumption seems to be warranted that the meager supply of chromidial substance present in the majority of the ganglion cells in most of the preparations in my series indicated over-stimulation. In most of the patients in question, hyperactivity of the sympathetic ganglion cells also was indicated by the secretory activity of the sweat glands of the cold extremities and the hypertonus of the musculature of the peripheral blood vessels which, before operation, resulted in diminution of the blood supply to the extremities.

In some of the cases in the series the abundant infiltration of the interstitial tissue in the ganglions with wandering cells, probably lymphocytes and mononuclear leukocytes, strongly suggested the existence of a chronic inflammatory process in the ganglions, which might be regarded as a stimulating factor. On the other hand, in diseases such as chronic polyarthritis, it is unnecessary to assume that the hyperactivity of the sympathetic ganglion cells is due to stimulation which arises within the ganglions. The sweat secretory activity and the vasoconstriction in the extremities could be accounted for on the basis of reflex responses through the sympathetic nerves to stimulation of sensory end-organs in the vicinity of the inflamed joints. The afferent impulses in question reach the spinal cord via somatic afferent fibers where they activate preganglionic neurons through the usual somatovisceral reflex connections. The vasoconstriction in the extremity brought about in this manner in turn doubtless aggravates the inflammatory processes in the vicinity of the joints. It also is conceivable that the peripheral sweat secretory and vasoconstrictor neurons may become hyperactive by reason of medulliadrenal hyperactivity, hyperirritability of the visceral centers

in the central nervous system or inflammation of the sympathetic ganglions resulting from intoxications or infectious processes not primarily associated with the joints.

Patients with certain vasomotor neuroses, e. g., Raynaud's disease, exhibit a more or less constant hypertonus of the arteries, particularly the arterioles of the extremities, in the absence of apparent peripheral inflammation, and this is aggravated by subjection of the extremities to low external temperature. In cases of this sort the hypertonus of the peripheral arteries indicates hyperactivity of the sympathetic neurons supplying the extremities or of the corresponding visceral centers in the central nervous system. The vasoconstrictor hyperactivity, regardless of whether it is a causative factor in the disease process in question or merely an accompaniment of the disease, may play an important rôle in the course and sequelae of the disease, particularly by reason of its effect on the blood pressure and the distribution of the blood volume in the body.

As previously stated, many of the ganglion cells in nearly all of the ganglions in the series under discussion contain melanotic pigment. According to Dolley[10] (1917) and Dolley and Guthrie[11] (1918), in experimental animals the accumulation of pigment in nerve cells is always associated with chronic functional depression. These investigators were unable to produce pigmentation in nerve cells by stimulation ranging from normal activity to functional senility. The accumulation of pigment in the autonomic ganglion cells in man doubtless can be explained most satisfactorily on the assumption that it is associated with functional depression of the ganglion cells. In spite of this assumption, however, the presence of pigment in many of the ganglion cells in most of the ganglions in the present series is not incompatible with the theory that other changes in the ganglions are associated with hyperactivity of the ganglion cells. Melanotic pigment is a highly stable substance, which, having been deposited in ganglion cells, may remain there indefinitely. A moderate amount of pigment in ganglion cells therefore need not be regarded as indicative of the functional state of the cells. It probably indicates only a previous state of functional depression. In general, it may be stated that the accumulation of pigment in the autonomic ganglion cells increases with advancing age. In rare instances, however, heavily pigmented ganglion cells have been observed in young individuals. Ganglion cells heavily laden with pigment are probably

10. Dolley, D. H.: The Recovery from Depression in the Purkinje Cells and the Decline of Senility of Depression; with the Incidental Histogenesis of Abnormal Pigmentation, J. Comp. Neurol. **28**:465, 1917.

11. Dolley, D. H., and Guthrie, F. V.: The Pigmentation of Nerve Cells, J. M. Research **34**:123, 1918.

always deficient in chromidial substance. Some of these doubtless represent cells which are no longer functional.

The shrunken hyperchromatic ganglion cells present in my preparations conformed very closely in cytologic structure to Dolley's [12] (1913) description of hyperchromatic neurons in the central nervous system, particularly Purkinje cells in the cerebellum, in a state of physiologic depression. The lighter staining ganglion cells in my preparations which exhibited hyaline changes in the cytoplasm also conformed more or less closely, in cytologic structure, to Dolley's description of physiologically depressed hypochromatic Purkinje cells. According to Dolley's observations physiologic depression of the nerve cells results in cessation of the production of chromidial substance in the cytoplasm, accumulation of chromatin in the nucleus and a shift in the nucleus-plasma ratio in favor of the nucleus. If the neuron contains an abundance or an excess of chromidial substance when depression sets in, discrete chromidial granules become less and less apparent, and the acid-staining elements of the cytoplasm become more and more evident. The chromidial substance in the cytoplasm gradually is consumed, and that which remains becomes finely granular or goes into solution. In erythrosin-toluidine-blue preparations, the cytoplasm assumes a diffuse blue or reddish color, depending on the degree of change, and, particularly in the later phases of depression, a hyaline appearance. If the neuron contains only a meager supply of chromidial substance when physiologic depression sets in, the cytoplasm may assume a hyaline appearance without the intense staining reaction.

In view of the cytologic resemblance of the shrunken hyperchromatic ganglion cells and many of the lighter-staining ganglion cells showing evidence of hyalinization of the cytoplasm in my preparations to neurons of experimental animals known to be in a state of physiologic depression, it seems not improbable that the changes referred to in these cells were indicative of physiologic depression. As previously stated, ganglion cells exhibiting these changes were present in only small numbers in most of my preparations, whereas the majority of ganglion cells present afforded evidence of overstimulation. Shrunken hyperchromatic ganglion cells also may be observed in preparations of the sympathetic ganglions of normal animals (cats). The presence of physiologically depressed ganglion cells in small numbers in the sympathetic ganglions should therefore probably not be regarded as indicative of the functional state of the sympathetic nerves.

Certain substances, e. g., toxins, which in dilute solutions stimulate ganglion cells, in less dilute solutions depress these cells. It is therefore

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12. Dolley, D. H.: The Morphology of Functional Depression in Nerve Cells and Its Significance for the Normal and Abnormal Physiology of the Cell, J. M. Research **29**:65, 1913.

not inconceivable that some ganglion cells, under appropriate conditions, may be depressed by the agents responsible for the stimulation of the majority of the ganglion cells in the same ganglions.

The existence in relatively large numbers of ganglion cells which exhibited evidence of physiologic depression in the preparations of the ganglions of certain patients in the present series strongly suggested that physiologic depression of sympathetic ganglion cells was related to the diseases in question, in these cases, or to other pathologic processes present. It was doubtless significant that of the patients with Raynaud's disease and chronic polyarthritis, i. e., diseases with which peripheral vascular hypertonus and other manifestations of sympathetic hyperactivity, e.g., hyperhidrosis, are known to be associated, the preparations of the ganglions of only one exhibited ganglion cells showing evidence of physiologic depression in large numbers. The case record of this patient also afforded evidence of toxicity. The existence of melanotic pigment in many of the ganglion cells and the presence of numerous ganglion cells showing other evidences of physiologic depression in the ganglions of the patient, who was 11 years of age and who had progressive muscular dystrophy, strongly suggested, in the absence of a record of other significant pathologic conditions, that physiologic depression of sympathetic ganglion cells, in this case, was related to the disease in question. The existence of numerous ganglion cells showing evidence of physiologic depression in the ganglions of the patient with paralysis agitans does not warrant the conclusion that physiologic depression of sympathetic neurons is related to this disease, since this patient gave a history of inflammatory rheumatism and sleeping sickness. The patient with endarteritis, preparations of whose ganglions exhibited many ganglion cells showing evidence of physiologic depression, as previously stated, also gave a history of alcoholism and addiction to drugs. The assumption that physiologic depression of the sympathetic neurons was related to the endarteritis, in this case, therefore, is unwarranted. Regardless of the possible relationship of physiologic depression of sympathetic ganglion cells to the disease process in certain cases in the present series, the total histopathologic picture of the ganglions could not be regarded as specific for the disease in question in any of these cases.

It seems not improbable that some of the swollen ganglion cells as well as those which underwent advanced neuronophagia in the present series of preparations had ceased to be functional. These, however, constituted only a small percentage of the total number of ganglion cells, the loss of which probably was functionally insignificant.

As stated in the preceding section of this paper, the histopathologic changes observed in the preparations of the sympathetic ganglions in this surgical series belong to the same general categories and cannot be

regarded as specific for the disease in question in any case. The case records of most of the patients in our series also indicated the existence of pathologic conditions not directly related to the disease in question, either preceding the latter or coincident with it. The changes observed in the preparations of the ganglions, therefore, at least in some of the cases, doubtless were associated with other pathologic conditions, as well as with the disease for which sympathectomy was carried out. As the histopathologic changes observed in most of the sympathetic ganglions in our series are indicative of hyperactivity of the ganglion cells, however, it seems not improbable that these changes and the associated autonomic dysfunction played a rôle in the disease processes in question, at least in those cases in which vasoconstriction was a factor in the disease. Possibly, physiologic depression of sympathetic ganglion cells, in those cases in which it is evident in a large percentage of the ganglion cells, also played a rôle in the disease process in question.

SUMMARY

All of the preparations of cervical and lumbar sympathetic ganglions removed surgically from thirty patients exhibited histologic changes which probably deviated from the range of normal variations. These changes included infiltration of the interstitial tissue with wandering cells, mainly lymphocytes and mononuclear leukocytes, the presence of free cells within the capsules of many of the ganglion cells, neurono-phagia of some of the ganglion cells, diminution of the chromidial substance in the cytoplasm of a large percentage of the ganglion cells, deposition of melanotic pigment in a variable percentage, marked edema of a small number and, in some cases, hyaline degeneration and vacuolation of ganglion cells.

The presence of wandering cells in large numbers in the interstitial tissue in some cases was regarded as evidence of chronic inflammation in the ganglions, which probably affected the functional state of the ganglion cells. The diminution of the chromidial substance in the ganglion cells probably was associated with hyperactivity of these cells. The presence of a moderate amount of pigment in ganglion cells was not regarded as indicative of the functional state of the cells; it probably indicated a previous state of physiologic depression. Marked shrinkage of hyperchromatic ganglion cells, disintegration of the chromidial bodies and hyaline changes in the cytoplasm were regarded as indicative of physiologic depression of the cells.

The changes observed in the ganglions in individual cases were not specific and could not be related directly to the disease in question. The functional states of the ganglion cells with which these changes were associated, however, probably played a rôle in the disease process.

LOCAL ATROPHY OF BONE

I. EFFECT OF IMMOBILIZATION AND OF OPERATIVE PROCEDURES

J. ALBERT KEY, M.D.

ST. LOUIS

FREDERICK FISCHER, M.D.

DETROIT

AND

EUGENE ELZINGA, M.D.

FLINT, MICH.

Fractures and operative procedures which are followed by prolonged immobilization of an extremity lead to a variable degree of atrophy of the bones of the extremity. This atrophy may be an important factor in the prolonged disability which often follows such injuries or operations. The observations recorded in this paper were made in an effort to determine whether or not atrophy of the bones will occur if a normal extremity is immobilized and whether the atrophy which follows fractures and operations is due to the immobilization or is due to the injury and changes in the circulation incident to the healing of the injury.

The various types of general and local atrophy and resorption of the bones have been considered elsewhere.[1] For the maintenance of normal structure of the bones it is necessary that an animal consume and utilize an adequate diet and that the bone be subjected to normal use. Deficient diet or abnormal metabolism leads to general atrophy of the bones, and disuse leads to local atrophy.

In spite of the general acceptance of the term "atrophy of disuse" as applied to bone, the knowledge of the occurrence of atrophy in normal extremities which have been immobilized rests on very few observations. This subject was studied in laboratory animals by Grey and Carr [2] and by Allison and Brooks.[3] In most of their experiments the disuse was

1. Key, J. A.: Bone Atrophy and Absorption, Internat. J. Orthodont. 15:949, 1929; Factors in Atrophy of Bone, J. Am. Dent. A. 17:1660, 1930. Key, J. A.; Elzinga, E., and Fischer, F.: Local Atrophy of Bone: II. Effect of Local Heat, Massage and Therapeutic Exercise, Arch. Surg., to be published.

2. Grey and Carr: An Experimental Study of the Factors Responsible for Noninfectious Bone Atrophy, Bull. Johns Hopkins Hosp. 26:381, 1915.

3. Allison and Brooks: Bone Atrophy, an Experimental and Clinical Study of Changes in Bone Which Result from Nonuse, Surg., Gynec. & Obst. 33:250, 1921.

obtained by sectioning the nerves to the extremity. In the light of theories that atrophy of the bones is caused by increased circulation (Pommer [4] and Leriche and Policard [5]) a limb which has been paralyzed by section of the nerves cannot be considered normal. However, Grey and Carr immobilized one extremity of each of two rabbits in a plaster of paris cast, and Allison and Brooks immobilized one extremity of each of four dogs in a plaster of paris cast. In each instance the bones of the immobilized extremity became atrophic. The observers concluded that the changes which occurred in the bone were practically the same as those which occurred in the paralyzed limbs, and that it made no difference whether the disuse was caused by plaster casts or by section of the motor nerves to the part.

The lack of definite observations on the occurrence of atrophy of the bones in normal extremities is perhaps one reason why the atrophy which occurs after fractures and operations on the extremities is often ascribed to the injury or operation rather than to the lack of use. The same is true of the atrophy which occurs in limbs in which tuberculosis or some other chronic disease exists. Is the atrophy of the bones due to the disease itself, to hyperemia induced by the disease or to lack of use?

EXPERIMENTAL WORK

In an attempt to answer the question as to whether or not immobilization in a plaster cast will cause atrophy of the bones in a normal extremity in a human being, we selected ten patients who were in the hospital for some condition of the upper extremities and who had normal lower extremities. With the patients' consent we applied comfortable plaster of paris casts to both lower extremities. The casts were bivalved and were strapped on. As we were using these patients to determine the effects of various forms of physical therapy on atrophy of the bone, the casts were removed twice a day while one limb was subjected to baking or massage or exercise. The routine was continued for from four to six weeks.

The presence of and the degree of atrophy were determined by studying roentgenograms of the feet. Lateral roentgenograms of each foot were made at the beginning of the experiment and again at the end of the period of immobilization. In order that the roentgenograms might give a true picture of the changes which occurred in the bones the length of the exposure, the position of the foot and the distance of the tube were kept as uniform as possible. The uniformity of the roentgenograms was further controlled by noting the density of the shadow cast by the soft tissues. We assumed that the density of the soft tissues did not change perceptibly during the period of immobilization, and we discarded those roentgenograms in which the shadows of the soft tissues were not approximately the same as those in the controls of the same foot taken before the period of immobilization.

Comparison of the roentgenograms showed that at the end of six weeks definite atrophy of the bones had occurred in the normal feet which had been immobilized.

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4. Pommer, G.: Origin and Diagnostic Significance of Osteoporosis, Arch. f. klin. Chir. **136**:1, 1925.

5. Leriche, R., and Policard, A.: Physiology of Bone, translated by Moore, Sherwood, and Key, J. A., St. Louis, C. V. Mosby Company, 1928, p. 81.

Fig. 1 (R. M.).—The left foot: *A*, before immobilization, and, *B*, after eight weeks of immobilization in a plaster of paris cast.

Fig. 2 (R. M.).—The right foot: *A*, before immobilization, and, *B*, after the Hoke operation and eight weeks of immobilization in a plaster of paris cast. The control foot is shown in figure 1.

This atrophy was evidenced by a diffuse rarefaction of all the bones of the foot and the lower ends of the tibia and fibula which were included in the roentgeno-grams. As a result of the rarefaction the shadows cast by the bones were less dense and the trabeculae stood out more clearly in the roentgenograms made at the end of the period of immobilization. This change was most clearly visible in the os calcis, astragalus, scaphoid and cuboid bones.

Having determined that atrophy of the bones does occur in normal extremities which are immobilized, and having obtained a fair idea of the amount of change to be expected, we selected forty patients who were to be subjected to various types of operation on the lower extremities and obtained lateral roentgenograms of the feet before operation and at periods of from four to twelve weeks after opera-tion. In several instances in which one foot was normal, we examined this foot roentgenologically before the operation, immobilized it in a plaster cast and studied it again by roentgen ray at the end of the period of observation. Thus we had a normal control on the same person. In other instances we used as controls the normal feet referred to in the preceding paragraph.

The majority of the patients had stabilizing operations on the feet, but osteot-omies for the correction of deformities, manipulations for clubfoot, arthrodeses of the hip or knee and operations on the soft tissues were included in the series.

Studies of the roentgenograms of the extremities operated on revealed definite atrophy in the bones of the feet. This could be detected in the roentgenograms taken four weeks after operation, but was more marked in those taken after ten or twelve weeks. In the postoperative roentgenograms of feet which had been immobilized for twelve weeks the trabeculae were smaller in diameter and less numerous than in the preoperative roentgenograms of the same feet. It thus appears that many trabeculae may be resorbed within the short space of three months. However, comparison of the roentgenograms of the feet of the extremities on which operation had been done with those of normal extremities which had been immobilized in plaster of paris casts over the same period of time led to the conclusion that there was approximately the same amount of atrophy in each. In other words, the atrophy of the bones was caused by the immobilization, and the operations on the bones or soft tissues of the extremity did not appreciably alter the rate or degree of the atrophy.

There was one exception. This occurred in a boy who had an osteotomy at the knee for the correction of a flexion deformity which had been caused by septic arthritis. Pyogenic infection appeared in the wound after the operation and an abscess and considerable fever developed. In this case the atrophy of the bones in the left foot (on which the operation was done) was definitely more pronounced than it was in the right (normal) foot. This one case indicates that the presence of an acute pyogenic infection may accelerate the resorption of the bones in that extremity as compared with that which occurs in the normal extremity which is immobilized but is not infected.

In several of the extremities on which an operation was done a variable amount of atrophy was present in the bones of the foot before the operation. In these the final roentgenograms showed an increase in the atrophy. The increase was propor-tional to the period of immobilization, and appeared to be independent of the state of the bone when the immobilization was started. Thus, atrophy of disuse is a progressive phenomenon, and when an extremity in which the bones are atrophic is immobilized there is a further resorption of the bones of this extremity.

In addition to the observation of atrophy of the bones in older children, we studied roentgenograms of the feet of younger children taken before and after immobilization, and found that the immobilization with or without surgical inter-
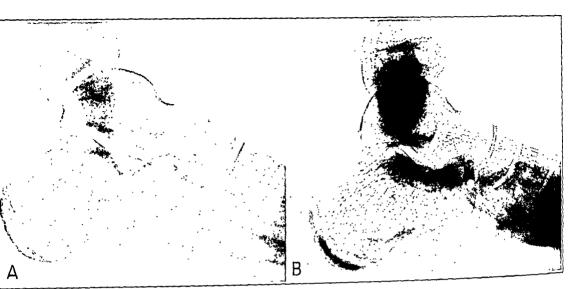
Fig. 3 (L. C.).—The right foot: *A*, before immobilization, and, *B*, after ten weeks of immobilization in a plaster of paris cast.
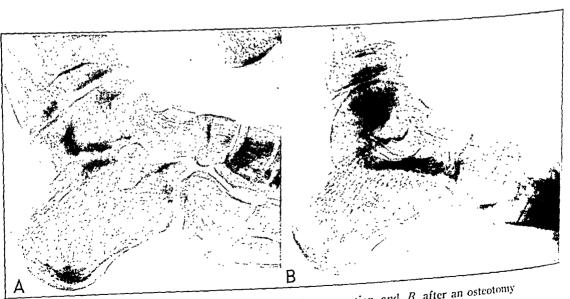
Fig. 4 (L. C.).—The left foot: *A*, before operation, and, *B*, after an osteotomy at the knee and ten weeks of immobilization in a plaster of paris cast. The operative wound became infected. The bone atrophy is more pronounced in this foot than in the control foot shown in figure 3.

vention or manipulation of the foot caused atrophy of the bones just as it did in older children. We were interested to note, however, that the later roentgenograms of the feet of the younger children showed a definite increase in the size of some of the centers of ossification in the bones of the tarsus, and in some instances new centers of ossification appeared. It is thus evident that formation of new bone may proceed in an extremity simultaneously with progressive resorption. In the older children, as a rule, no difference could be detected in the size of the bones, but in certain instances the apophysis of the os calcis was definitely larger in the later roentgenograms with atrophy than it was in the preoperative roentgenograms before the atrophy began. We have made no observations on the rate of growth of bone during the period of immobilization, but the clinical observation that the bones of a limb which had been subjected to a long period of disuse during the period of growth are apt to be shorter and smaller than those in the opposite limb indicates that lack of use tends to decrease the rate of growth in the bones of an extremity, but does not completely arrest growth.

COMMENT

It may be objected that the immobilization of a limb in a plaster of paris cast has a definite effect on the circulation in the extremity and that any change which occurs in the limb cannot be attributed merely to the lack of use, but is more likely the result of a change in the circulation of the part. It is true that the circulation in a limb which is immobilized in a plaster cast is not normal. But we have no reason to believe that the circulatory change is due to the cast. It is probably due to the lack of use of the muscles of the part and to the lack of normal strain of bearing weight. Furthermore, there is no evidence to indicate that this change in the circulation is the cause of the atrophy of the bones. If the atrophy were due to circulatory changes the atrophy would be more marked in extremities which have been subjected to accidental or to operative trauma, with resultant marked changes in the circulation. Since we have shown that practically the same degree of atrophy occurs in the bones of extremities in which surgical intervention has occurred as in normal extremities which are immobilized, we believe that the atrophy exhibited in our cases was due to the lack of use and that it was not due to any increase or decrease of the circulation.

However, we do not ignore or attempt to explain the acute atrophy of the bones which may occur after an injury. This acute traumatic atrophy of Sudeck has not been produced experimentally and its mechanism is unknown. It may be due to local circulatory changes which are more marked than those which occur after an operation, but it is more reasonable to believe that the acute atrophy of the bones which occasionally follows an injury and which usually occurs in the vicinity of an infection is due to some chemical alteration in the fluids of the tissues in the involved area.

CONCLUSIONS

1. Immobilization of an extremity leads to atrophy of the bones of this extremity.

2. This atrophy can be detected in roentgenograms taken four weeks after the immobilization began.

3. The atrophy is progressive, and if an extremity with atrophic bones is immobilized, further atrophy of these bones may be expected.

4. Operative or accidental trauma does not appreciably increase the atrophy incident to the immobilization.

5. The presence of a pyogenic infection in the extremity appears to increase the local atrophy of the bones.

6. The growth and formation of new bone may occur simultaneously with local atrophy of a given bone.

LOCAL ATROPHY OF BONE

II. EFFECT OF LOCAL HEAT, MASSAGE AND THERAPEUTIC EXERCISE

J. ALBERT KEY, M.D.

ST. LOUIS

EUGENE ELZINGA, M.D.

FLINT, MICH.

AND

FREDERICK FISCHER, M.D.

DETROIT

During the past fifteen years physical therapy has assumed an important place in the armamentarium of physicians, and large amounts of time and money are expended in administering various forms of physical therapy to patients who are ill or who are convalescing from disease or from accidental or operative injuries. Naturally a considerable literature has accumulated on the subject, but the observations are largely clinical and are not carefully controlled. Consequently, the beneficial effects claimed for various physical therapeutic procedures cannot be accepted without reservations, because due allowance must be made for the enthusiasm of the physician and for the desire of the patient to get well, while little credit is given to the natural tendency of the injured tissues to heal and resume their normal functions.

As a matter of fact, a large percentage of the physical therapy which is used today is prescribed and administered empirically. This is particularly true of the baking, massage and exercises which are regarded by many as the sine qua non for the efficient care of patients who have suffered injuries of the bones or joints or who have been subjected to orthopedic operations. This empiricism is due to the lack of carefully controlled experimental work, and the lack of experimental work is due to the fact that administration of physical therapy to laboratory animals is laborious and estimation of the results is difficult, while the opportunity for making adequately controlled observations on patients does not often present itself.

The extensive studies of Hartman, Blatz and Kilborn [1] are a notable exception. These observers showed that massage and active contractions

1. Hartman, F. A.; Blatz, W. E., and Kilborn, L. G.: Studies in the Regeneration of Denervated Mammalian Muscle: II. Effect of Massage, J. Physiol. **53:** 108, 1919; III. Effects of Massage and Electrical Treatment, ibid. **53:**290, 1919; IV. Effects of Massage and Electrical Treatment in Secondary Sutures, ibid. **54:**392, 1920.
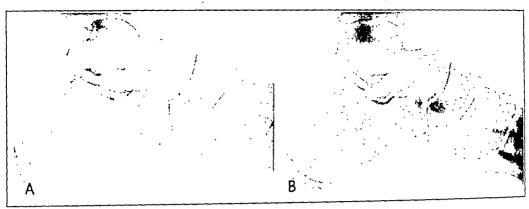
Fig. 1 (P. T.).—The left foot: *A*, before immobilization, and, *B*, after six weeks of immobilization in a plaster of paris cast.
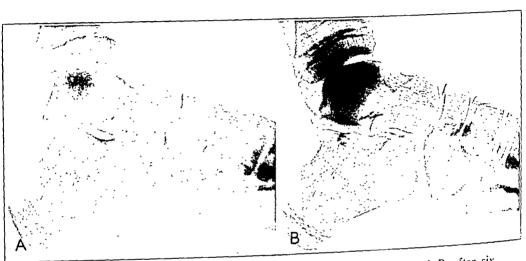
Fig. 2 (P. T.).—The right foot: *A*, before immobilization, and *B*, after six weeks of immobilization in a plaster of paris cast. The foot and leg were massaged twice a day during the period of immobilization. The control is shown in figure 1.

Fig. 3 (J. D.).—The right foot: *A*, before immobilization, and, *B*, after six weeks of immobilization in a plaster of paris cast. This foot and leg were baked twice a day during the period of immobilization.

of the muscles induced by a slow surging galvanic current had no bene-
ficial effect on the soleus, gastrocnemius and plantaris muscles of rabbits
which had been paralyzed by cutting the sciatic nerves.

We shall attempt to evaluate the effects of heat, massage and thera-
peutic exercise on bones in which local atrophy was being induced by
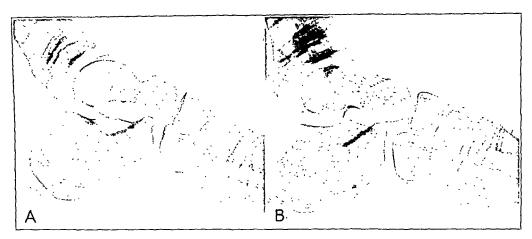
Fig. 4 (A. R.).—The left foot: A, before immobilization, and B, after six
weeks of immobilization in a plaster of paris cast.
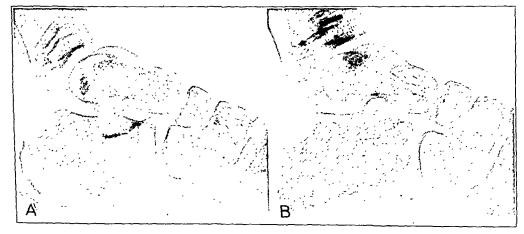
Fig. 5 (A. R.).—The right foot: A, before immobilization, and, B, after six
weeks of immobilization in a plaster of paris cast. This foot was exercised twice
a day during the period of immobilization. The control is shown in figure 4.

disuse, and in a later paper we hope to evaluate the effects of the same
procedures on normal muscles which are being rendered atrophic by
disuse. Having established the facts that if the normal lower extremity
of a child from 10 to 12 years of age is immobilized in a plaster of Paris

cast for a period of from four to twelve weeks, the bones of the immobilized foot will become atrophic, and that this atrophy will progress at such a rate that it can be detected in roentgenograms of the foot taken four weeks after the beginning of the immobilization, we were in a position to study the effect of massage, local heat and therapeutic exercise on bone. Consequently, the following experiment was undertaken:

EXPERIMENTAL WORK

Ten patients with normal lower extremities and no general disease were selected. These were patients of suitable age who were willing to cooperate in the experiment and who were in the hospital for the treatment of some deformity or paralytic condition of one or both upper extremities. The experiment did not prolong their stay in the hospital or work any undue hardship on them.

Each lower extremity, with the foot at a right angle to the leg and the knee slightly flexed, was encased in a comfortable plaster of paris cast which extended from the toes to the upper third of the thigh. After the plaster had hardened the casts were bivalved and strapped on. The left lower extremity was used as the control and the right lower extremity was subjected to baking, massage or exercise. In five of the ten patients, the right lower extremity was baked, in two massaged and in three exercised.

In order to make the control as exact as possible the cast was removed from the left lower extremity while the physical therapy was being given to the right lower extremity. The experiments lasted for six weeks, and the physical therapy was given twice a day. Uniform roentgenograms of both feet in two planes were taken at the beginning and at the end of the experiment.

The degree of atrophy of the bones which occurred was estimated by comparing the roentgenograms taken before and after the period of six weeks. It was found that the lateral view of the foot and ankle was most satisfactory and that the astragalus, os calcis, scaphoid and cuboid were the bones which showed the most constant changes. Decrease in the density of the bones as a whole, decrease in the size and number of the trabeculae and decrease in the thickness of the cortex were considered evidence of atrophy. The relatively slight degree of atrophy which was produced by immobilization for six weeks was characterized by decrease in the density of the bones as a whole; the changes in the size and number of the trabeculae were relatively slight, while no changes could be detected in the thickness of the cortex. The decrease in the density of the bones caused the trabeculae to stand out more clearly in the atrophic bones.

At the end of the experiment the children were permitted to resume their normal activities. The movement in the joints and power in the muscles were soon restored without specific treatment, and the patients suffered no ill effects from the period of immobilization.

RESULTS

Local Heat.—The local heat was applied in the form of dry (radiant) heat supplied by an ordinary electric baker with carbon light bulbs. The right foot and lower part of the leg were placed in the baker for twenty minutes twice a day. Comparison of roentgenograms taken at the end of the period with those taken before the experiment began

showed that definite atrophy of the bones occurred in all of the feet which were immobilized and that the atrophy was of practically the same degree in the bones of the control limbs as in those which were baked.

Massage.—The massage was administered to the right leg and foot by a trained physical therapist and was continued for ten minutes twice a day. Comparison of the roentgenograms taken before and at the end of the experiment showed that atrophy of the bones occurred in all of the immobilized feet and that this atrophy was of practically the same degree in the controls as in those which were massaged.

Exercise.—The exercises were as follows: "1. Raise the right leg as high as possible with the knee straight, and lower it. 2. Flex the right hip and knee as far as possible; then extend the leg on the thigh and lower the foot to the bed. 3. Dorsiflex the foot and curl the toes; then plantarflex the foot and curl the toes. Do each exercise slowly twenty-five times, twice a day." The physical therapeutist was responsible for the execution of the exercises as prescribed. Comparison of the roentgenograms taken before and at the end of the experiment showed that atrophy of the bones occurred in all of the immobilized feet, and the degree of atrophy was practically the same in the bones of the control limbs as in those which were exercised.

COMMENT

The observations recorded in this paper are not presented as evidence that it is not possible to affect atrophy of the bones by physical therapy, but are presented as evidence that baking, massage and exercise in the amounts in which these measures are used clinically have no appreciable effect on the local atrophy of the bones which is caused by immobilization of the part.

It is probable that no amount of massage or passive movement which could be tolerated by the patient would have any appreciable effect on the atrophy. However, if the voluntary muscular exercises were carried out more frequently it would be possible to lessen or to prevent atrophy of the bones, in which case there would be little immobilization or disuse. In regard to local heat, we believe that this tends to accelerate the atrophy incident to disuse. We have seen patients with local atrophy of the bones which we believe was partly caused by the enthusiastic and prolonged use of baking or of diathermy.

CONCLUSION

Short periods of local heat, massage or active exercise have little, if any, effect on local atrophy of the bones which occurs when an extremity is immobilized in a plaster of paris cast.

DISTENTION OF THE URINARY BLADDER

I. HEMATURIA AND SUDDEN EMPTYING; AN EXPERIMENTAL AND CLINICAL STUDY

C. D. CREEVY, M.D.

MINNEAPOLIS

Sudden emptying of the chronically distended urinary bladder, especially in prostatic hypertrophy, has been condemned as hazardous for so long that the idea has become a tradition. The Ebers papyrus gives a prescription to prevent the too rapid escape of urine.[1] The conception that one must withdraw the urine slowly first received wide recognition early in the nineteenth century. It was then gradually lost to view, only to reappear with the comparatively recent development of prostatic surgery.

I recently reviewed the literature dealing with the reaction to rapid decompression of the distended bladder; at this time only the portion which refers to the relationship of rapid decompression and bleeding will be reviewed in detail. The most widely accepted explanation of the supposed danger of rapid emptying of the bladder in cases of chronic retention maintains that the intravesical pressure is elevated as a result of the retention. This elevated tension is alleged to be transmitted to the kidneys. The blood vessels of the urinary tract are said to adapt themselves to the heightened pressure, so that the sudden withdrawal of the urine leads to prompt dilation of the vessels with rupture and hemorrhage into the tissues and lumens of the urinary tract. The congestion and hemorrhages thus produced are assumed to interfere with the renal function to the point of causing uremia and even death.

While this makes an admirable theory, it is by no means so free from objection as one might be led to believe from a casual survey of the literature. It is only recently that its soundness has been questioned. Prätorius[2] said not long ago that he had never seen a case of this

1. Garrison, F. H.: An Introduction to the History of Medicine, Philadelphia, W. B. Saunders Company, 1921.

2. Prätorius, G.: Ueber die erstmalige Behandlung hochgradiger Harnverhaltungen, Deutsche med. Wchnschr. 55:875, 1929.

ex vacuo bleeding. Bazy [3] declared that the distended bladder should be emptied promptly and kept empty. Brecher and Chwalla,[4] after a study of three hundred cases, concluded that gradual withdrawal of the urine possesses no advantages over simple catheterization; the latter procedure does not appear to increase the incidence of hematuria or of untoward reactions of any kind. Rose [5] observed that he could see no objection to rapid withdrawal of the urine provided the bladder is kept empty thereafter. I [6] recently analyzed a series of seventy-one cases which came to autopsy after catheterization for urinary retention due to prostatic hypertrophy. I was forced to conclude that rapid emptying of the bladder is of itself harmless, and that gradual decompression, far from possessing advantages, may even be dangerous in that it prolongs the period of inadequate drainage with its attendant increased liability to infection. The following objections to the idea that the sudden relief of chronic or subacute retention is harmful were found:

1. Other sources of hematuria are available in prostatism; it has been shown both experimentally and clinically that these may, alone or in combination, cause the various phenomena seen after sudden relief from obstruction.

2. No incontrovertible proof exists that sudden emptying of the bladder can of itself produce bleeding or other untoward reactions.

3. Death following catheterization is due almost invariably to an infectious process, either renal (80 per cent) or extrarenal (20 per cent).

4. Hematuria may fail to follow catheterization in circumstances which would certainly produce it if it were due to mechanical factors.

5. Bleeding accompanies gradual as well as sudden evacuation of the urine.

6. That a constant elevation of the intravesical tension exists in obstruction remains to be shown. That is, it is not certain that spontaneous decompression does not occur.

7. Gradual, as compared to sudden, decompression has not lowered the mortality of patients catheterized for retention of the urine from prostatic enlargement. Two series of cases, alike except for the rate of emptying of the bladder, were compared; they showed no difference in the mortality following treatment.

3. Bazy, P.: Note sur la pathogénie, le diagnostic, et le traitement des pyélonéphrites suppurées, Bull. et mém. Soc. d. chirurgiens de Paris **22**:263, 1896.

4. Brecher, E., and Chwalla, R.: Neues zur Behandlung der Harnretention nebst Untersuchungen über die Entlastungsreaktion, Ztschr. f. urol. Chir. **31**:266, 1931.

5. Rose, D. K.: Clinical Application of Bladder Physiology, J. Urol. **26**:91, 1931.

6. Creevy, C. D.: The Effect of Sudden Emptying of the Chronically Distended Bladder, Arch. Surg. **25**:356, 1932.

CAUSE OF THE HEMATURIA

Leaving aside the propriety of sudden, as compared with gradual, emptying of the chronically distended bladder, it is interesting to inquire as to the possible cause of the bleeding which so often follows the catheterization of patients with chronic partial urinary retention.

The literature names four possible causes other than complications like neoplasm and urolithiasis, namely, urinary retention, sudden emptying of the bladder, infection and trauma.

Retention of Urine.—This can of itself cause hematuria; the presence of vascular congestion and engorgement in the prostate, bladder, ureters and kidneys of patients with obstruction at the vesical outlet has been known for years and commented on by many observers, among them Mercier [7] (1861), Grellety,[8] Picard,[9] Tuffier,[10] Genouville and Boeckel,[11] Delbet,[12] Chute [13] and Vintici and Laroche [14] 1929). They attribute the congestion to venous stasis resulting from an increase in the intravesical tension. Its existence is verified clinically by the frequent occurrence of bleeding following even the gentlest urethral manipulation in patients with prostatic obstruction.

This stasis in prostatic retention may produce hemorrhage into the urinary tract, since Bernard,[15] Albarran,[16] Sedillot,[17] Escat,[18] Walker,[19]

7. Mercier, A.: Note sur l'hématurie qui suit le cathétérisme dans quelques cas de rétention d'urine, Union méd. de Paris **9**:41, 1861.

8. Grellety, M.: Mécanisme des accidents mortels qui dans certains cas accompagnent l'évacuation trop prompte de la vessie, France méd. **25**:146, 1879.

9. Picard, M.: Les dangers du cathétérisme chez les vieillards, *France méd.* **26**:106, 1879.

10. Tuffier, T.: Rôle de la congestion dans les maladies des voies urinaires, Thèse de Paris, 1885, p. 149.

11. Genouville, M., and Boeckel, A.: Physiologie pathologique du cathétérisme, in Pousson, A., and Desnos, E.: Encyclopedie française d'urologie, Paris, Gaston Doin & Cie, 1914, vol. 4, p. 944.

12. Delbet, P.: Rétention et incontinence d'urine, in Pousson, A., and Desnos, E.: Encyclopédie française d'urologie, Paris, Gaston Doin & Cie, 1914, vol. 6, p. 492.

13. Chute, A. L.: Observations on Cases of Prostatic Obstruction Presenting Overdistended Bladders, Boston M. & S. J. **167**:607, 1912.

14. Vintici, V., and Laroche, A.: Hemorrhagies de la prostate, J. d'urol. **28**:140, 1929.

15. Bernard, M. C.: A Simple Method of Relieving Retention of the Urine in Diseases of the Prostate Gland, Dublin M. J. **17**:369, 1847.

16. Albarran, J.: Etude sur le rein des urinaires, Thèse de Paris, Paris, Jouve & Cie, 1889.

17. Sedillot, C.: Des accidents graves qui suivent parfois le cathétérisme et les autres opérations pratiquées sur l'urétère, Gaz. d. hôp. **4**:546, 1861.

18. Escat, J.: Des hématuries rénales chez les prostatiques, Thèse de Paris, 1897, p. 1.

19. Walker, K. M.: The Risks of Prostatectomy, Practitioner **112**:278, 1924.

Young [20] (3.6 per cent of nine hundred and eighty-three cases or 14.1 per cent of those with large amounts of residual urine), Bumpus and Foulds [21] (5 per cent of eighty-three patients with distended bladders) and Vintici and Laroche [11] encountered bleeding in apparently uncomplicated prostatic hypertrophy.

Further proof that urinary retention may cause hematuria is found in the literature on experiments. Guyon and Albarran [22] and, later, Shigematsu [23] ligated the urethra in dogs and rabbits, thereby producing hemorrhages at first in the vesical submucosa, later in the detrusor urinae and finally in the renal parenchyma.

Other evidence is found in the fact that ligature of the ureter also causes bleeding. Fabian [24] (guinea-pig), Corbett [25] (dog) and Helmholz and Field [26] (rabbit) observed bleeding into the renal parenchyma and into the wall and lumen of the pelvis within eighteen hours of experimental ureteral occlusion.

Sudden Emptying of the Retained Urine.—This has always been regarded as productive of hematuria, but the actual importance of this factor is difficult to evaluate. Desormeaux [27] drew an analogy between postcatheterization and postpartum bleeding, although, since the retained urine is not attached by a placenta the separation of which leaves a raw surface, this analogy is impossible. Le Grand,[28] Guyon [29] and Blum and Rubritius [30] spoke of hemorrhage *ex vacuo,* but failed to explain how a vacuum may develop in a collapsible organ with flexible

20. Young, H. H.: Hydraulic Pressure in Genitourinary Practice, Especially in Contracture of the Bladder, Bull. Johns Hopkins Hosp. **9**:100, 1898; Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 17.

21. Bumpus, H. C., Jr., and Foulds, G. S.: Gradual Emptying of the Overdistended Bladder, J. A. M. A. **81**:821 (Sept. 8) 1923.

22. Guyon, J. F., and Albarran, J.: Anatomie et physiologie pathologique de la rétention d'urine, Arch. de méd. expér. et d'anat. **2**:181, 1890.

23. Shigematsu, H.: Etude expérimentelle de la rétention d'urine, J. d'urol. **25**:16, 1928.

24. Fabian, E.: Die Niere des Kaninchens nach der Unterbindung ihres Harnleiters, Biblioth. med. Abt. Path. u. path. Anat. **18**:1, 1904.

25. Corbett, J. F.: Changes in the Kidney Resulting from Tying the Ureter, Am. J. M. Sc. **144**:568, 1912.

26. Helmholz, H. F., and Field, R. S.: Acute Changes in the Rabbit's Kidney, Particularly the Pelvis, Produced by Ligating the Ureter, J. Urol. **15**:409, 1926.

27. Desormeaux, M.: Hemorrhagie vésicale mortelle à la suite du cathétérisme, Bull. et mêm. Soc. d. chirurgiens de Paris **50**:743, 1851.

28. Le Grand, A.: Union méd. de Paris, 1860, p. 471; quoted by Mercier.[7]

29. Guyon, J. F.: Rétention d'urine: Forme aiguë et forme chronique, Gaz. d. hôp. **52**:481, 1879.

30. Blum, V., and Rubritius, H.: Klinik der Prostatahypertrophie, in von Lichtenberg, A.; Voelcker, F., and Wildbolz, H.: Handbuch der Urologie, Berlin, Julius Springer, 1926, vol. 5, p. 585.

walls. Countless writers have attributed vesical and renal hemorrhage (Young [20] has seen bloody urine issuing from the ureters after catheterization of the distended bladder) to the emptying alone, but have failed to consider the objections just named.

Other potent objections exist. First, gradual emptying of the bladder does not protect against bleeding. Van Zwalenburg's [31] patient bled; so did 5 per cent of the eighty-three patients of Bumpus and Foulds,[21] as well as 48.7 per cent of the patients in thirty-three fatal cases which I reported.

Moreover, the relief of enormous vesical distentions may fail to cause hemorrhage. Lund, Corner [32] and Bury [33] each reported a case of chronic, partial retention due to incarceration of a retroflexed gravid uterus; they withdrew 13,960, 4,000 and 4,900 cc. of urine, respectively, without causing bleeding. Pinkham [34] and Hamman [35] reported the removal of 7,900 and 7,000 cc. from elderly patients with prostatism without bleeding.

If postcatheterization bleeding is actually due to mechanical factors (a fall of tension with bursting of the vessel walls), these discrepancies are difficult to explain. If, on the other hand, it is due to other factors, such as trauma or infection, the explanation is easy. The wide variations in the amount of trauma from catheterization are too obvious to require comment; variations in the virulence of bacteria and in the susceptibility of the hosts are part of everyday knowledge.

Rôle of Infection.—The rôle of infection in the production of hematuria has been underestimated.

Goodhart [36] was apparently one of the first to realize that urinary retention predisposes to infection (1873). He found renal abscesses at autopsy in 20 per cent of a large series of patients with obstruction of the neck of the bladder and the urethra. This clinical observation was soon supported experimentally by Albarran,[16] Rovsing,[37] Melchior [38] and

31. Van Zwalenburg, C.: Emptying a Chronically Distended Bladder; Description of a Simple Device, J. A. M. A. **75**:1711 (Dec. 18) 1920.

32. Corner, M. C.: An Interesting Case of Retention to the Amount of a Gallon, Lancet **2**:130, 1905.

33. Bury, B. W.: A Case of Retention of Urine, Brit. M. J. **1**:936, 1911.

34. Pinkham, J. G.: Distention of the Bladder Mistaken for Ascites, M. Rec. **10**:1065, 1875.

35. Hamman, D. J. H.: Extreme Bladder Overdistention, Brit. M. J. **1**:141, 1906.

36. Goodhart, J. F.: On Erysipelas of the Kidney and Urinary Tract, Guy's Hosp. Reports **19**:357, 1873-1874.

37. Rovsing, P.: Pathogenese und Behandlung der septischen Infektion der Harnwege, Monatsbl. d. Krankh. d. Harn.-u. Sex.-Appar. **3**:506, 1898.

38. Melchior, M.: Berichte über 52 bakteriologisch untersuchte Fälle von infectiösen Erkrankungen der Harntracte, Monatsbl. d. Krankh. d. Harn.- u. Sex.-Appar. **3**:584, 1898.

others. Rovsing and Melchior also called attention to the fact that trauma, like retention, increases the liability of the urinary tract to bacterial invasion.

Infection, either alone or in combination with retention, can cause severe bleeding. Albarran [16] pointed out that often the only demonstrable lesion in early acute pyelonephritis consists of leukocytic infiltration and of hyperemia or hemorrhage. Escat [15] reported the finding of a hydronephrosis filled with blood, in which the cause of the bleeding was a bacterial inflammation. Koch,[39] using the staphylococcus, and Sweet and Stewart,[40] using Bacillus coli, produced hemorrhages into the renal parenchyma in association with a suppurative nephritis following the intravenous injection of these organisms. The frequency of severe hematuria during acute glomerulonephritis, which is bacterial in origin, is familiar to every physician.

Hemorrhage coincident with the onset of infection in the course of prostatic obstruction has been reported by Escat,[18] Chute,[13] Hyman, Elfving [41] and me.[6]

Instrumental Trauma.—Trauma caused by instruments also may lead to bleeding in the patient with prostatic obstruction. Indeed, it was at first blamed for the fatal reactions following catheterization (Finlayson [42] and Tuffier [10]); Escat [18] said that he had never seen hematuria follow an easy, gentle catheterization. While trauma undoubtedly plays a part in the production of postcatheterization bleeding, it can scarcely be regarded as the sole cause, particularly since patients who die of such reactions usually, if not invariably, exhibit renal lesions, and since Young [20] saw blood issue from the ureters of patients who were bleeding after catheterization. As only a small percentage of patients with uncomplicated prostatic obstruction bleed spontaneously, other explanations have been sought.

EXPERIMENTAL AND CLINICAL STUDY

In order to present a fairly complete chain of evidence as to the origin of postcatheterization bleeding in urinary retention, five series of experiments were performed. Series 1 consisted of twelve dogs in

39. Koch, J.: Ueber die Hämatogene Entstehung der eitrigen Nephritis durch den Staphylokokkus, Ztschr. f. Hyg. u. Infektionskr. **61**:301, 1908.

40. Sweet, J. E., and Stewart, L. F.: Ascending Infections of the Kidney, Surg., Gynec. & Obst. **8**:460, 1914.

41. Elfving, A. K.: Ueber Blutdruck und Nierenfunktion der Prostatiker, Acta Soc. med. fenn. duodecim **9**:1, 1928.

42. Finlayson, J.: Case of Extensive Submucous Ecchymosis in the Bladder and Hemorrhage into the Tubules of the Kidney, Occurring Within Two Days from a Single Catheterization, Glasgow M. J. **21**:132, 1884.

which simple acute retention of the urine was established, the animals being killed and examined at intervals thereafter.

In series 2 comprising eight animals, the conditions of the first group of experiments were duplicated, except that after an interval the retention was relieved. The animals were killed later.

Series 3 consisted of two dogs in which a chronic partial urinary retention was established by incomplete urethral ligature. In both animals hematuria developed; they were included to demonstrate the relationship of hematuria to infection engrafted on obstruction. This series was reenforced by the inclusion of a number of clinical cases.

Series 4 comprised six dogs, in which the procedure mentioned in connection with the first group was carried out, but in addition the spinal cord was sectioned in the middorsal region in order to observe the effect of distention of the bladder without voluntary attempts to urinate.

In series 5 the bladders of four animals were distended rapidly with comparatively high pressures under anesthesia, while the abdomen was open. In four more animals, stretching of the vesical wall was prevented by enclosing the bladder in a rigid bag.

Series 1: Simple Acute Retention as a Cause of Hematuria.— Twelve normal male dogs, varying in weight from 12 to 16 Kg., were used. After tests had shown that the urine and the nonprotein nitrogen of the blood were normal, the animals were anesthetized by the subcutaneous injection of morphine sulphate supplemented by the local injection of 0.5 per cent procaine hydrochloride. Under sterile conditions, the penis was then isolated in the perineum behind the bone, its vessels were stripped off and preserved, and the urethra was occluded by a ligature of linen tape. The animals were then allowed to recover in metabolism cages. Only those that passed no urine while the ligature was in place were included in this study. They were allowed to eat and drink at will. This series of experiments was divided into three groups.

The first group consisted of three dogs killed with chloroform twenty-four hours after occlusion of the urethra; the second group comprised six dogs killed after forty-eight hours, and the third, three dogs killed after from sixty to seventy-two hours.

After the retention had lasted for the required period, the animals were anesthetized with chloroform, the abdomen opened and the bladder inspected. A sterile large-caliber needle was inserted into the bladder through the anterior wall, and the intravesical pressure was recorded by means of a vertical glass tube. Urine was then aspirated for culture, measurement and urinalysis. The anesthesia was then deepened until death occurred; autopsy was performed.

Certain animals died; similar observations were made except that the pressure and the ability of the bladder to contract during emptying could not be observed.

EXPERIMENT 1.—In a male dog weighing 18 Kg., with a twenty-four hour acute retention, the nonprotein nitrogen one hour before death was 17 mg. for each 100 cc. of blood. The bladder held 625 cc. of sterile urine which contained a few red blood cells; the intravesical tension was 4 cm. of water, and the viscus contracted on being emptied. At autopsy the thoracic and abdominal cavities showed nothing abnormal except the distended bladder. Histologically, the kidneys and ureters were normal. There were a few small hemorrhages beneath the vesical mucosa, which was intact (fig. 1).

Fig. 1 (experiment 1).—Early hemorrhage into the wall of the bladder resulting from obstruction for twenty-four hours.

EXPERIMENT 2.—In a male dog weighing 12 Kg., with a twenty-four hour obstruction, the antemortem nonprotein nitrogen was 20 mg. per hundred cubic centimeters. The bladder was cyanotic and contained 560 cc. of sterile urine, in which several red blood cells were found in each high power field. The pressure was 18 cm. of water. When the bladder was emptied, its color returned to normal. Autopsy revealed nothing unusual. Microscopic examination of the kidneys, ureters and bladder revealed nothing abnormal.

EXPERIMENT 3.—A male dog weighing 15 Kg., with a twenty-four hour retention, was given 1,000 cc. of a physiologic solution of sodium chloride subcutaneously following urethral ligature; the dose was repeated on the following morning. The nonprotein nitrogen was 25 mg. before death. The bladder contained 805 cc. of faintly turbid, sterile urine with many red blood cells and a few white cells in each high power field. The bladder was plum-colored and markedly distended; the tension was 21 cm. of water. The discoloration disappeared as the bladder

contracted on being emptied. On section, one saw in the kidneys a mild engorgement of the vessels of the medulla which could not be regarded as abnormal. The ureters showed no changes. Beneath the vesical mucosa, particularly in the posterior midline, were several hemorrhages varying from 0.5 to 3 mm. in diameter, and a few submucous petechiae scattered over the base and dome (fig. 1).

Comment.—In three normal male dogs, ligation of the urethra for twenty-four hours produced no definite renal lesions except in one animal (experiment 3); here the picture was that of engorgement of the capillaries and of the veins which was not sufficiently marked to justify conclusions. The bladder was regularly the seat of a few small hemorrhages beneath the mucosa, particularly in the midline of the posterior wall. The distended bladder appeared cyanotic, but returned to its normal color on being emptied. The nonprotein nitrogen of the blood did not rise, nor were abnormally formed elements other than a few red cells found in the urine.

These results are in contrast to those of Guyon and Albarran [22] and of Shigematsu,[23] who regularly found small hemorrhages in the kidney and a rise in the nonprotein nitrogen of the blood (the blood in the urea was found by Guyon and Albarran; the rise in the nonprotein nitrogen, by Shigematsu) twenty-four hours after obstruction of the urethra. However, these findings were to be anticipated for several reasons:

1. The urinary output of dogs given a constant intake of fluid is extremely irregular. At the outset of these experiments it was intended to make estimations of the renal function by determination of the chemical constituents of the urine before, during and after retention without catheterization. It was found that, in a series of ten dogs given a constant intake of 500 cc. every twenty-four hours and a weighed diet of ground beef the daily output of urine varied from 50 to 1,200 cc., while the chemical constituents of the urine varied within equally wide limits. These discrepancies are evidently due to the male dog's habit of emptying the bladder incompletely.

2. On several occasions, during abdominal operations on dogs of average size with undisturbed urinary tracts, I have seen bladders holding as much as 1,300 cc. in the absence of evidence of obstruction.

3. Dogs kept in cages void less often than those allowed to run about, evidently in anticipation of freedom. It may be that the dogs studied by Guyon and Albarran were not caged and therefore tried to void more often than the animals which were caged.

It was therefore expected that a twenty-four hour obstruction would not produce lesions unless, as in experiment 3. fluids were forced.

Because definite damage did not appear in this group of animals, the second group of six dogs with obstruction of approximately forty-eight hours' duration was studied.

EXPERIMENT 4.—A dog weighing 20 Kg. died forty-eight hours after ligature of the urethra. The nonprotein nitrogen of the blood was 125 mg. three hours before death. Autopsy revealed the presence of bronchopneumonia. The kidneys and ureters were engorged. The bladder was plum-colored and distended with 800 cc. of sterile urine containing many white cells. When the bladder was emptied post mortem, the color of its external surface returned practically to normal, but the wall remained flaccid and wrinkled. There were, however, numerous elevated hemorraghic areas with raised margins, particularly on the posterior wall, on the mucosal aspect.

On microscopic examination, the kidneys showed patchy areas in which the epithelium of the convoluted tubules and of Henle's loop were swollen and vacuolated, partially occluding the lumens, which in many areas contained hyaline and granular casts. These areas were most numerous immediately beneath the renal
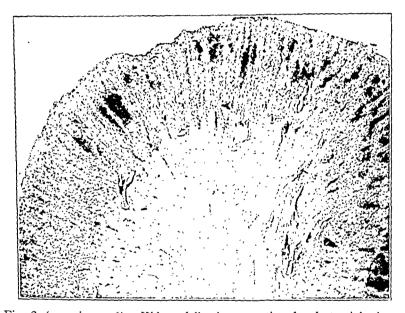
Fig. 2 (experiment 6).—Kidney following retention for forty-eight hours.

capsule. The vessels about the collecting tubules were choked with blood, and there were a few small hemorrhages beneath the pelvic mucosa, which was intact. The ureters were normal.

The bladder showed many large hemorrhages beneath the mucous membrane. The mucosa was missing over many of these areas, and a few of the hemorrhages extended into the muscular coat for a short distance.

EXPERIMENT 5.—In a male dog weighing 20 Kg. the nonprotein nitrogen was 80 mg. after a forty-eight hour retention. The dog was anesthetized. The bladder held 1,300 cc. of sterile urine containing a few red and white blood cells. The external surface of the bladder was plum-colored, but it became practically normal when the bladder was emptied. Contraction was incomplete. At autopsy, in addition to the presence of lesions like those seen in experiment 4, there were a few small cortical hemorrhages which adjoined the swollen tubules. The ureters were normal, while the bladder showed the changes seen in the preceding experiment.

7, on the other hand, there was an advanced lesion in the kidneys characterized by radial linear hemorrhages passing through the medulla and the cortex and associated with marked necrosis in adjoining tubules, while the bladders were necrotic. It is also to be noted that in experiment 3 a retention of 800 cc. produced only a little damage within twenty-four hours, while a retention of 800 cc. in experiment 4 produced more marked changes in forty-eight hours, although dog 3 weighed only 15 Kg. and its bladder was therefore relatively less distended than that of dog 4, which weighed 20 Kg.

EXPERIMENT 10.—A male dog weighing 16 Kg. died seventy hours after urethral ligature. The nonprotein nitrogen forty-eight hours after ligature was 45 mg.; after seventy-two hours, 60 mg. Autopsy, which was performed immedi-
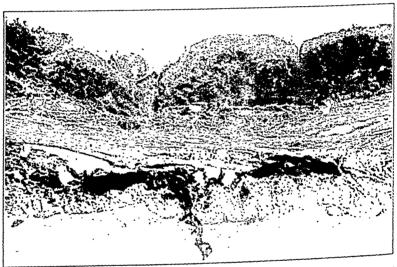
Fig. 5 (experiment 6).—Advanced hemorrhages into the wall of the bladder following retention for forty-eight hours.

ately after death, revealed purulent bronchopneumonia. The bladder was distended and plum-colored, and contained 300 cc. of turbid but sterile urine, with albumin, many red blood cells, a moderate number of white cells and many granular casts. There was no return to normal color, and the bladder did not contract after emptying. The kidneys were moderately softened and hemorrhagic. The ureters were normal. Microscopic examination revealed many small, peritubular hemorrhages in the cortex. Adjoining the hemorrhages were a few areas in which the tubules were swollen, with pale, vacuolated cytoplasm containing shrunken, deeply-staining nuclei. The bladder showed submucosal hemorrhages with invasion of the muscularis and mucosa, and necrosis.

EXPERIMENT 11.—A dog weighing 20 Kg. died seventy-four hours after urethral ligature. The bladder contained 1,000 cc. of sterile urine, in which innumerable red blood cells and a few white cells were found. The bladder was flaccid and blue-black; at the apex was a tear 3 cm. in diameter, from which the necrotic mucosa protruded. There was a tiny opening in the mucosa from which bloody urine escaped, thus explaining 800 cc. of bloody peritoneal fluid. The

peritoneum was everywhere intensely congested and exhibited small, fibrinous plaques. There were numerous hemorrhages in the free margin of the great omentum which was applied to the rent in the bladder. The kidneys showed lesions like those described in experiment 9. The lower one third of each ureter was moderately dilated. Microscopic examination of the kidneys revealed the typical radiating hemorrhagic streaks with necrosis of adjoining tubules and hemorrhages beneath the pelvic mucosa. The ureters contained small adventitial hemorrhages. The bladder exhibited numerous hemorrhages infiltrating the entire muscular wall, associated with sloughing of the overlying mucosa and necrosis of the invaded muscle.

EXPERIMENT 12.—A male dog weighing 28 Kg. was found dead sixty-eight hours after urethral ligature. The observations were similar to those in the preceding dog except that there was more advanced peritonitis, with 1,500 cc. of bloody urine in the abdominal cavity. The bladder was flaccid, gangrenous and empty, and there was a large perforation at the apex.

Comment.—Plainly the lesions of experimental acute retention are variable. After twenty-four hours the most prominent change observed was mild cyanosis of the vesical wall which disappeared on emptying of the bladder. A few small, submucous hemorrhages were seen, but the ureters and kidneys were normal. Within forty-eight hours the changes were intensified. The cyanosis was more striking, and large extravasations of blood invaded the bladder wall, especially posteriorly in the midline, where the blood supply was poor. Hemorrhagic lesions appeared also in the ureters and kidneys. In from sixty to seventy-two hours the bleeding into the bladder wall produced necrosis with rupture and urinary peritonitis. The rupture was always in the same situation. The lesions in the upper urinary tract were similarly more advanced.

Series 2: Rôle of Sudden Emptying of the Acutely Distended Bladder in the Production of Hematuria.—This series consisted of eight animals. The operative procedure was identical with that in the first series. After the obstruction was established, the animals were placed in metabolism cages and observed to make sure that no urine was passed. The obstruction was relieved after twenty-four, forty-eight and seventy-two hours by removal of the ligature. A catheter was passed, and the bladder pressure measured. All of the animals voided. Twenty-four hours later they were killed with chloroform and studied.

EXPERIMENTS 13 and 14.—In two animals weighing 18 and 19 Kg., respectively, the obstruction was relieved under local anesthesia after twenty-four hours. The bladder tensions were 17 and 23 cm., respectively. The urine which was voided at the time of the removal of the ligature contained a few red cells but was sterile. The urine which was subsequently passed was clear. The animals were killed twenty-four hours after ligature. No lesions were demonstrable at autopsy.

EXPERIMENT 15.—In an animal weighing 14 Kg. the obstruction was relieved without anesthesia after forty-eight hours. The pressure was 24 cm. The dog promptly voided 600 cc. of bloody, sterile urine. He was chloroformed twenty-four hours later. He had voided 1,000 cc. in the interval. The urine cleared grossly during this period; the last specimen voided before death contained a moderate

number of red blood cells. At autopsy the bladder held 50 cc. of smoky urine containing numerous red cells. In all other respects the observations at autopsy coincided with those in experiment 6.

EXPERIMENT 16.—In a male dog weighing 18 Kg. the tension was 30 cm. after a forty-eight hour retention. After removal of the ligature without anesthesia the animal voided 800 cc. of bloody sterile urine, and in the ensuing twenty-four hours 500 cc., the amount of blood in each successive specimen being less than that in the preceding one. At autopsy 25 cc. of smoky, sterile urine was observed. The bladder wall was hemorrhagic in the usual situation. There were mucosal petechiae. The kidneys were mildly engorged.

EXPERIMENT 17.—In a male dog weighing 14 Kg., after relief of a retention of seventy hours' duration, 200 cc. of bloody, sterile urine escaped under a pressure of 8 cm. of water, but the bladder was still palpable. Two hundred cubic centimeters of bloody urine was passed the ensuing day. The animal was anesthetized twenty-four hours after the removal of the ligature. The bladder wall was cyanotic and wrinkled and collapsed without contracting on the removal of 400 cc. of bloody urine. At autopsy the whole posterior wall was necrotic but intact. The ureters were dilated in their lower third, while the kidneys presented the picture seen in experiment 6.

EXPERIMENT 18.—In a male dog weighing 15 Kg., the obstruction was relieved sixty-eight hours afterward because the bladder was so distended that rupture was feared. Five hundred cubic centimeters of bloody urine at a pressure of 12 cm. was passed at once, leaving the bladder slightly distended. One thousand cubic centimeters was passed in the following twenty-four hours, with gradual clearing of the urine. At postmortem examination twenty-four hours after the relief of the retention, the bladder was contracted and hemorrhagic, and there was necrosis of the posterior wall. The ureters were slightly dilated at their lower ends; the kidneys were congested and showed radial streaks of hemorrhage.

Comment.—Sudden relief of acute urinary retentions of twenty-four, forty-eight, sixty-eight and seventy-two hours' duration did not produce results differing from those seen after simple retention. There was a marked tendency toward recovery, even within twenty-four hours, except in dog 17, in which the intramural hemorrhage was so advanced as to prevent muscular contraction. It seems evident, therefore, that at least in acute urinary retention the sudden relief of pressure is without undesirable effects. To test this observation further, experiments 19 and 20 were performed.

EXPERIMENT 19.—A dog weighing 21 Kg., immediately on the release of the ligature seventy hours after its application, voided 900 cc. of bloody urine under a pressure of 20 cm. The urine was sterile and contained red blood cells in gradually diminishing amounts for three days; it became normal on the fourth day, when the animal was killed. At autopsy the bladder contained 10 cc. of clear urine. The external surface was normal except posteriorly, where there was a hemorrhagic patch the size of a quarter. The ureters appeared normal, as did the kidneys.

Microscopically, the hemorrhagic area in the bladder wall was surrounded and invaded by leukocytes; the red cells had lost their outlines; a few fibroblasts were seen at the edges. The kidneys showed radially arranged streaks in which groups

of tubules were surrounded by leukocytes and young connective tissue; the epithelium of the tubules was basophilic and swollen and contained deep-staining nuclei.

EXPERIMENT 20.—In a male dog weighing 17 Kg. the obstruction was relieved seventy-two hours after ligation. The tension was 10 cm. Two hundred cubic centimeters of sterile bloody urine was evacuated at once; the bladder remained palpable. The dog voided 800 cc. during the ensuing twenty-four hours. At forty-eight hours the urine contained a few red blood cells. At seventy-two hours it was microscopically normal, and it remained normal until the animal was killed on the twenty-ninth day. Nothing abnormal was found at autopsy. Microscopic examination of the kidneys showed scattered radial streaks of connective tissue extending from the calices to the capsule and corresponding to the hemorrhagic bands seen in the early lesions. Adjoining the connective tissue an occasional tubule showed
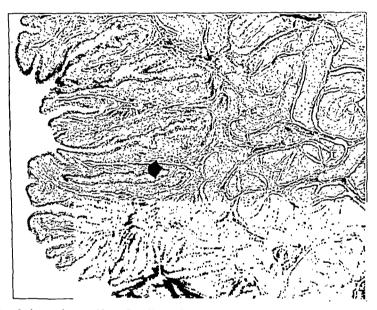
Fig. 6 (experiment 20).—Healing of the bladder twenty-nine days after severe damage. Only a few collections of lymphocytes show the site of the original lesion.

a few pale, faintly basophilic cells with flattened epithelium and deeply stained nuclei.

The bladder (fig. 6) showed only a few small collections of lymphocytes scattered through the interstitial tissue and penetrated, in a few areas, by young connective tissue cells.

Comment.—It is clear that sudden relief of an acute retention is harmless, since the animals recover.

Series 3: Relationship of Infection of the Urinary Tract to Hematuria.—In this series two experiments on dogs and two cases in man illustrated the relationship of hematuria to infection in the urinary tract.

EXPERIMENT 21.—A female dog weighing 28 Kg. showed normal urine. A valve was constructed of metal in such a manner as to allow fluid to pass through in a small stream. The valve was sterilized, inserted into the urethra and held in place by a tight ligature of linen tape surrounding the entire urethra. The dog voided slowly thereafter. Six weeks later urination was slow, difficult and frequent. Hematuria appeared and increased so rapidly in severity that within seven weeks after the operation the urine was extremely bloody. An enormously distended bladder was felt at this time.

The animal was killed with ether forty-five days after the operation. The bladder was distended and plum-colored. It contained 1,200 cc. of bloody urine. The mucosa was gangrenous. The metal valve had disappeared. Its former site was occupied by filiform stricture. The ureters and renal pelves were moderately dilated and edematous. The kidneys were increased in size. The parenchyma was softened and engorged. On section innumerable evenly distributed miliary abscesses were seen.

EXPERIMENT 22.—This experiment was identical with the foregoing except that the valve with the linen ligature around it was found in the bladder; the urethra contained a filiform stricture.

Comment.—The first two series showed clearly that acute urinary retention alone can produce hemorrhage into the urinary tract. The last two experiments prove that infection engrafted on chronic retention may produce or aggravate bleeding.

CASE 1.—A man, aged 72, said that he had had urinary difficulty of one year's duration. Prostatic hypertrophy was present. There was 20 cc. of sterile residual urine. Suprapubic cystostomy yielded a clear, sterile urine. The urine continued to be clear for seventy-two hours, when, coincident with a chill and a rise of temperature to 102 F., it became bloody. Culture then showed a streptococcic infection.

CASE 2.—A man, aged 72, had had difficult urination for several years. He had noticed a mass in the lower part of the abdomen three months before admission. Its appearance coincided with the onset of nocturnal incontinence. There was moderate diffuse enlargement of the prostate, and the bladder was palpable a fingerbreadth below the umbilicus.

Thirteen hundred cubic centimeters of clear, sterile urine was evacuated by suprapubic cystostomy. The urine remained clear for twenty-four hours, at which time the temperature rose to 100.4 F., and hematuria appeared. B. coli and streptococci were found on culture.

Comment.—In these cases there was hemorrhage from infection. In the first instance. there was only 20 cc. of residual urine. Seventy-two hours after the commencement of drainage, bleeding associated with bacteriuria appeared. Since decompression could not have occurred, the bleeding must be attributed to infection.

In the second case, the withdrawal of 1½ quarts (1.4 liters) of residual urine was followed by bleeding, but not until twenty-four hours afterward. How, except by an infectious process, can one account for the latent period?

The bleeding from trauma is too well known to require illustration, but a case illustrating the aggravation of bleeding by an acute pyelonephritis seems worthy of mention.

CASE 3.—A boy of 19 who had a contracted bladder secondary to a nontuberculous pyelonephritis of long standing bled during cystoscopy. Shortly thereafter he had a chill; the temperature rose to 103 F., and the bleeding increased. The blood ·rea rose to 90 mg., and the hemoglobin fell from 90 to 42, so that two days after the cystoscopy a transfusion was required.

Comment.—Hematuria in acute urinary retention may therefore originate from simple retention, from trauma or from infection (gangrenous cystitis or pyelonephritis). But what is the mechanism which produces the hemorrhage in simple retention? Is it a question of stretching of the bladder wall with, as has been suggested, tearing of the vessel walls, or is it a question of pressure? Series 4 and 5 were undertaken in an attempt to answer these questions.

Series 4-5: Origin of the Bleeding in Acute Urinary Retention.— The experiments in series 4 concerned the effect of stretching the bladder wall. Because of the varying effects of given retentions of similar duration it seemed probable that some factor other than contraction of the bladder wall must be concerned. It appeared not unlikely that this factor might be the attempts of the animal to empty the bladder. In order to test this theory, in six animals (experiments 23 to 28) the spinal cord was divided at the sixth dorsal segment in order both to prevent sensory impulses from the bladder from reaching the brain and to prevent straining (paralysis of the abdominal muscles). It was assumed that the well known reflex centers in the sacral cord (Budge,[43] Goltz,[44] Giannuzzi,[45] McClintic,[46] Mosso and Pellacani [47]) maintained the response of the bladder wall to distention in a fairly normal state.

EXPERIMENTS 23-24.—In two normal male dogs weighing 18 and 21 Kg. under ether anesthesia and with surgical asepsis, the sixth dorsal segment of the spinal cord was exposed and crushed with a ligature of linen tape surrounding the dura mater. Immediate paralysis of the hindquarters ensued. The urethra was ligated as described in connection with series 1. Forty-eight hours later the non-protein nitrogen of the blood was normal. No leakage of urine had occurred. Under chloroform anesthesia the bladders were exposed! They were distended but

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43. Budge, J.: Ueber das Centrum genitospinale des Nervus sympathicus, Virchows Arch. f. path. Anat. **15:**115, 1858; Zur Physiologie des Blasenschliessmuskels, Arch. f. d. ges. Physiol. **6:**306, 1872.

44. Goltz, F.: Ueber die Funktionen des Lendenmarks des Hundes, Arch. f. d. ges. Physiol. **8:**460, 1874.

45. Giannuzzi: Recherches physiologiques sur les nerfs moteurs de la vessie, J. physiol. de l'homme **6:**22, 1863.

46. McClintic, C. F.: The Clinical Neurophysiology of the Automatic Urinary Bladder and Enureses, J. Urol. **20:**267, 1928.

47. Mosso, A., and Pellacani, P.: Sur les fonctions de la vessie, Arch. ital. de biol. **1:**97 and 291, 1882.

of normal appearance, and contained 800 and 950 cc., respectively, of sterile, normal urine under pressures of 12 and 16 cm. The animals were killed. Autopsy showed nothing further. Microscopic examination of the kidneys, ureters and bladder showed no lesions.

EXPERIMENTS 25-26.— In two normal male dogs of 14 and 17 Kg. the same operative procedures as in experiments 23 and 24 were carried out. Seventy-two hours later the nonprotein nitrogen was normal. The bladders contained 1,100 and 1,550 cc., respectively, at tensions of 16 and 24 cm. of water. There was no discoloration of the external surface. The organs contracted normally on being emptied. The urine contained a few red cells and was sterile. The bladder showed a very few small petechiae beneath the mucosa. Microscopically, nothing else was found, the vesical muscle, the ureters and the kidney pelves being normal.

EXPERIMENTS 27-28.—In two dogs of 19 and 22 Kg. the operative procedures were identical with those in the foregoing experiments. There was no leakage of urine. Ninety-six hours after operation the nonprotein nitrogen of the blood was normal. The bladders were exposed. That of dog 27 contained 1,800 cc. of turbid, sterile urine at a tension of 23 cm. Its abdominal surface was slightly cyanotic but cleared when the bladder contracted on being emptied. The urine contained a moderate number of red blood cells. There were numerous petechiae in the vesical submucosa, but none in the muscularis. The kidneys and ureters were normal.

The observations in experiment 28 were similar to those in the preceding experiment. The bladder contained 2,150 cc. at a pressure of 15.5 cc.

Comment.—It seems clear, from the degree of distention seen and from the duration of these experiments, that simple stretching of the bladder wall for periods as long as four days does not suffice to cause severe damage to the vessels of the organ. However, on the fourth day damage begins.

The chief factor in the injury to the bladder was evidently the abnormal pressure generated therein during urinary retention. The effect of rapidly developed high pressures was tested in experiments 29, 30, 31 and 32.

EXPERIMENTS 29-32.—In four normal male dogs of 12, 16, 21 and 22 Kg. the bladder was distended rapidly through a fiber catheter, under ether anesthesia. The pressure was read after the injection of every 100 cc. of sterile physiologic solution of sodium chloride. Each injection required about three minutes. A small sample of fluid was aspirated from the bladder after each injection.

In each instance, when the resultant intravesical tension exceeded from 50 to 60 cm. of water (corresponding to an average content of 400 cc.), blood appeared in the samples of irrigating fluid. Examination of the bladder wall after the appearance of bleeding showed numerous petechial hemorrhages in the mucosa and submucosa. If the distention was continued beyond this pressure, bleeding increased and the muscularis became somewhat hemorrhagic, but no gross or microscopic lesions of the kidney or ureter developed.

Comment.—Slow distention of the urinary bladder produced hemorrhages into the bladder wall within forty-eight hours. Gangrene and perforation followed in from sixty to seventy-two hours. Section of the spinal cord inhibited the development of these lesions so that at ninety-six hours (four days) only submucosal hemorrhages were seen.

in spite of a tremendous distention of the organ. The evidence of series 4 shows that distention beyond a certain pressure causes hemorrhage. Is this due to stretching or to pressure? This question is answered by series 5.

In series 5 the effect of high intravesical pressure without stretching of the bladder wall was studied.

EXPERIMENTS 33 to 36.—In normal male dogs weighing from 15 to 21 Kg., the bladder was exposed under ether anesthesia and sugical asepsis and enclosed in a sterile bag of heavy, inelastic cloth having a capacity of 150 cc. Rapid distention of the bladders was carried out as outlined earlier. It was found that elevation of the pressure above 50 to 60 cm. of water produced mucosal and submucosal hemorrhages, and that these invaded the muscularis if the pressure was carried high enough.

COMMENT

Acute urinary retention causes bleeding into the tissues and cavities of the urinary tract. The factors which produce the bleeding require analysis.

As has already been noted, interference with the venous return was long ago blamed for the congestion and venous stasis in the entire urinary tract in prostatic hypertrophy. The same factor was regarded by Cohnheim [48] as responsible for the stasis of blood in the kidney following experimental ligature of the ureter. Lindemann [49] found that obstruction of the ureter increased the volume of the kidney; Lucas [50] and Newman [51] observed a diminution in the flow of blood from the renal vein during distention of the renal pelvis; and Hinman [52] showed

48. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, A. Hirschwald, 1880.

49. Lindemann, W.: Ueber die Wirkung der Gegendruckerhöhung auf die Harnsekretion, Beitr. z. path. Anat. u. z. allg. Path. 21:500, 1897.

50. Lucas, D. R.: On the Intraureteral Pressure and Its Relation to the Peristaltic Movements of the Ureter, Proc. Soc. Exper. Biol. & Med. 2:61, 1904; Studies of the Peristalsis of the Ureter in Dogs by the Graphic Method, Am. J. Physiol. 17:392, 1906-1907.

51. Newman, D.: Residual Urine and the Senile Bladder, Glasgow M. J. 87:73, 1917.

52. Hinman, F., and Morrison, D. M.: Experimental Hydronephrosis, J. Urol. 11:435, 1924. Hinman, F., and Hepler, A. B.: Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on its Rate of Development; Partial Obstruction of Renal Artery; Diminished Blood Flow; Diminished Intrarenal Pressure and Oliguria, Arch. Surg. 11:649 (Nov.) 1925; Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development, and Significance of Venous Collateral System; Partial Obstruction of Renal Vein Without and With Ligation of All Collateral Veins, ibid. 11:917 (Dec.) 1925; Experimental Hydronephrosis; Effect of Ligature of One Branch of Renal Artery on Its Rate of Development; Simultaneous Ligation of Posterior Branch of Renal Artery and Ureter on Same Side, ibid. 12:830 (April) 1926.

conclusively that hydronephrotic atrophy is the result of compression of the renal vessels by the distended pelvis.

This same factor appears to be responsible for the stasis of blood and later for the hemorrhage seen after occlusion of the urethra. This is shown by the congestion and cyanosis of the bladder wall, which appeared in every obstruction and which, in all except the most advanced cases, disappeared when the viscus was emptied. Further evidence is found in the location of the earliest as well as the most advanced hemorrhages in the advanced cases. They always appeared in and about the midline of the posterior wall above the trigon. Even a casual inspection of the dog's bladder shows that the blood supply is poorest at this point, a fact which indicates that a relatively slight increase in tension tends to cause damage. While these changes were attributed by Guyon and Albarran [22] to a reflex, such an explanation seems superfluous.

If urinary retention is long continued, certain secondary effects appear and aggravate the primary lesions. The first is necrosis, apparently due to deficient oxygenation secondary to interference with the blood supply by the hemorrhages; this appears within forty-eight hours and within from sixty to seventy-two hours is often sufficiently advanced to cause rupture.

The other secondary effect is functional. As has been pointed out by Guyon and Albarran, in acute retention the irritability of the bladder muscle is soon lost. In this series it disappeared in most of the experiments of forty-eight hours' duration and in all of those of from sixty to seventy-two hours' duration (experiments 10, 11, 12 and 17). It is not even then irreparable, as shown by the recovery of animals 18, 19 and 20.

These secondary effects (the first doubtless causes the second) appear to be responsible for the increased susceptibility to infection of the obstructed urinary tract. The necrotic tissue furnishes a culture medium the surface of which is isolated from the usual defenses against bacterial invasion; the loss of contractility causes incomplete emptying of the bladder. The resultant stasis favors bacterial growth.

Although a few hemorrhages in the bladder wall may appear within twenty-four hours, the kidneys are not involved for another day. This lag is undoubtedly due to the fact that reflux up the dog's ureter does not occur (Sampson,[53] Lucas,[50] Newman,[51] Draper and Braasch,[51] Bush

53. Sampson, J. A.: Ascending Renal Infection with Especial Reference to the Reflux of Urine from the Bladder into the Ureters, Bull. Johns Hopkins Hosp. **14**:334, 1903.

54. Draper, J. W., and Braasch, W. F.: The Function of the Ureterovesical Valve, J. A. M. A. **60**:20 (Jan. 4) 1913.

and McCradie,[55] Gruber,[56] Shigematsu[23] and others). The kidneys are thus protected for a time. Since the kidney and ureter together, however, may exert pressures of from 40 (Heidenhain[57]) to 76 mm. (Gottlieb and Magnus[58]) of mercury (54 to 103 cc. of water), and since the ureter alone may sustain a pressure of 67 mm. of mercury (92 cc. of water), a rise of tension in the bladder is soon met by a similar rise of tension in the ureter. Elevation of the intravesical tension is at first delayed by the tendency of the bladder (observed by Mosso and Pellacani,[47] Sherrington,[59] and others) to maintain a constant pressure regardless of the degree of distention (postural tone, Sherrington). This protective mechanism apparently fails at some time between twenty-four and forty-eight hours, when the intra-ureteral and intra-pelvic tensions become sufficient to cause venous (and perhaps arterial) compression, at first with stasis and later with hemorrhage. This hemorrhage into the kidney may cause serious anatomic (figs. 2 and 4) and functional impairment, the latter being shown by definite rises in the nonprotein nitrogen of the blood in experiments 6, 7, 8 and 10.

That the hemorrhagic lesions of the bladder are due to interference with the blood supply by the intravesical tension rather than to simple stretching and tearing seemed probable from the fact that the same lesions appeared later in the renal parenchyma where the degree of distention was probably insufficient to cause actual lacerations. This view was substantiated by the results of series 4 and 5, in which it was found that if efforts to urinate were prevented, great distention of the bladder did not damage that organ until the fourth day, at which time there were mild lesions. When one compares this with the fact that much less severe distention ruptured the bladder within seventy-two hours if the animal was allowed to strain, it was obvious that pressure, not stretching, damages the bladder wall. Final proof was obtained by subjecting the bladder to high pressure by the rapid injection of fluid, both under normal conditions and while it was enclosed in a small, inelastic bag which prevented stretching. Both procedures caused changes identical with but less extensive than those due to ligature of the urethra. The greater severity of the lesions of urethral ligature were doubtless due to the much longer duration of the latter.

55. Bush, A. D., and McCradie, R. S.: Competency of the Ureterovesical Valves, Am. J. Physiol. **68**:107, 1924.

56. Gruber, C. M.: The Function of the Ureterovesical Valve and the Experimental Production of Hydronephrosis, J. Urol. **23**:161, 1930.

57. Heidenhain, R.: Die Harnabsonderung, in Hermann, L.: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, 1881, vol. 5, pt. 1, p. 299.

58. Gottlieb, R., and Magnus, R.: Ueber Diurese, Arch. f. exper. Path. u. Pharmakol. **45**:223, 1901.

59. Sherrington, C. S.: Postural Activity of Muscle and Nerve: III. Visceral Muscle, Brain **38**:213, 1915.

No attempt was made to follow the fluid output during retention, as was done by Guyon and Albarran, because, as has already been pointed out, the fluid output of dogs is irregular even when the intake of water and food is constant.

The lesions of experimental acute retention are strikingly similar to those which have been attributed by many writers to sudden emptying of the chronically distended bladder. The hemorrhages, the hematuria, the renal insufficiency and the suppression of urine (Guyon and Albarran) are seen in both. These same changes can also follow acute pyelonephritis. I have shown that patients who die after catheterization die of infection, and that gradual emptying does not reduce the percentage of infective lesions or influence the mortality in similar groups of cases. Is it necessary, then, to retain the old belief that sudden emptying of the distended bladder is dangerous? I think not.

No effort has been made in this study to ascertain by what mechanism the rise in tension which damages the bladder is produced. The literature states that the contraction of the bladder wall produces the increased tension, but it is not certain whether this is wholly true. Certain observations made in the course of these experiments suggest that it is not. For example, in experiment 3 a retention of 800 cc. produced slight changes within twenty-four hours. In experiment 4 retention of the same amount caused more severe damage in forty-eight hours. Dog 3 weighed 5 Kg. less than dog 4 and was therefore relatively more distended. Furthermore, in experiment 10 a retention of 300 cc. caused advanced changes in seventy-two hours.

Aside from the important elements of time and degree of distention, there seems to be another factor which is responsible for the fact that a given retention in one animal may cause advanced changes, while in another it has only a slight effect. The response of smooth muscle to a given stimulus is so uniform as to lead one to seek some other explanation of the varying effects of urinary retention. This explanation is probably to be found in the influence of the contraction of the abdominal wall and the diaphragm (i. e., the voluntary attempts to urinate) on the bladder pressure. The influence of this factor on pressure in the normal bladder has been recognized by Mosso and Pellacani,[47] Dubois,[60] Adler,[61] Hirsch,[62] Kreutzmann, Rose[5] and others, but no attempt has been made to separate its effect in urinary retention from that of the

60. Dubois, P.: Ueber den Druck in der Harnblase, Deutsches Arch. f. klin. Med. **17**:148, 1876.

61. Adler, A.: Ueber den Druck in der Harnblase zugleich ein Beitrag zur Funktion des Blasenmechanismus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **50**:487, 1918.

62. Hirsch, E. W.: Relation of Bladder Pressure to Bladder Function, J. A. M. A. **91**:772 (Sept. 15) 1928.

contraction of the bladder wall. The question has been investigated, and observations will be reported in a subsequent study.

I have thus far had the opportunity of treating ten patients with marked vesical distention due to prostatic disease. The youngest patient was 50; the oldest, 78. One had a prostatic carcinoma; two had fibrous contractures secondary to prostatitis, and seven had prostatic hypertrophy. Four had incontinence (overflow) : three of three months' duration and one of a year's duration. Residual urines varied from 750 to 1,500 cc.

In all, abrupt emptying was practiced, in three with the catheter and in seven with suprapubic cystostomy. In four bleeding developed after a definite latent period and was associated with the development of bacteriuria and other evidence of pyelonephritis. In the others infection and bleeding were present on admission, the latter usually being due to previous catheterization; that it preceded the catheterization in the hospital was proved by the appearance of blood in the first drops of urine evacuated and by the presence of dark, clotted blood.

One patient so nearly reproduces experimental conditions as to deserve description in detail.

CASE 4.—C. G., a man, aged 69, had increased vesical irritability for several years. Twenty-four hours before admission he had acute retention. His physician made an unsuccessful attempt at catheterization, and then referred him to the hospital, where he arrived with a distended bladder. The prostate was moderately enlarged. Blood was dripping from the urethra. Attempts were made to pass first a soft rubber, and then a filiform, catheter. These failed. Suprapubic drainage evacuated 750 cc. of urine containing dark clots. Culture showed a gram-positive bacillus. The external surface of the bladder wall was a dusky, bluish red. The temperature remained normal for six days, and then rose to 103 F. for two consecutive days, following which it returned to normal. The patient was sent home with an apparatus for suprapubic drainage and asked to return later for treatment of the obstructing prostate.

In this patient, all three of the factors sharing responsibility for bleeding in acute urinary retention, namely, prolonged complete retention, trauma and infection, were present. The bleeding cleared up promptly with free drainage. Treatment of the obstructing gland was deferred because the striking similarity in the appearance of the bladder of this patient to that of the dog with experimental retention suggested that considerable necrosis had occurred.

One experiment that would probably settle permanently the question whether sudden emptying of the distended bladder can of itself produce bleeding has not been performed. It consists of measuring the actual loss of blood in a series of patients who have been relieved or of measuring urinary retention by the indwelling catheter or by a suprapubic tube without any attempt at gradual decompression, and in comparing the amount to that in a similar series in which gradual

decompression has been practiced. This can be done by removing the blood from the urine with the centrifuge and converting the hemoglobin to acid hematin, from which the volume of blood actually lost can easily be reckoned.

Because of the relatively infrequent admission of suitable cases to a small urologic service, the investigation of this subject will require a number of years.

SUMMARY

The literature bearing on the relationship between hematuria and urinary retention as well as infection in the urinary tract has been briefly reviewed. It has been pointed out that the inconstancy of the occurrence of hematuria following sudden emptying of the bladder suggests that some factor other than the mechanical one of sudden emptying must be involved. It has been pointed out that in fatal cases the lesions following gradual catheterization are identical with those developing after sudden emptying, and that the mortality for sudden emptying of the bladder is almost identical with that for gradual withdrawal. These facts suggest that the rate of emptying of the distended bladder may not be responsible for the train of events which sometimes follows catheterization and of which hematuria is usually described as typical.

It has also been pointed out that trauma and infection may play important rôles in postcatheterization bleeding. Illustrative cases and two experiments with animals have been cited.

A series of thirty-six experiments on dogs has been performed and has shown that:

1. Acute retention interfered with the venous return from the urinary tract. This effect was seen earliest in the bladder, where it led to hemorrhage and necrosis in the area of poorest blood supply. .

2. The upper urinary tract was at first protected both by the tendency of the bladder to relax as it fills and by the absence of reflux of the urine into the ureters.

3. Between twenty-four and forty-eight hours after the establishment of retention the pressure in the bladder became elevated. The kidney and ureter then generated pressures sufficiently high to impair their own blood supply.

4. It has been shown experimentally that the critical factor which leads to injury of the bladder wall during urinary retention is not the stretching with tearing of the vessels but the rise of pressure, which may be quite independent of the volume of urine.

5. The venous stasis and hemorrhages into the upper urinary tract led to impairment of the renal function after a latent period of twenty-four hours.

6. Sudden relief of the obstruction did not of itself produce lesions but led to recovery.

7. The varying intensity of lesions produced by a given degree of distention or by distention for a given period suggested that some mechanism less constant than the contraction of the bladder wall produced the rise in intravesical tension. This appeared to be the action of the diaphragm and abdominal muscles (attempts to void). A study of their relative rôle has been made, and it will be reported in part II of this paper.

8. A series of ten cases of retention due to prostatism in which ill effects did not follow sudden withdrawal of the urine by catheter (three cases) or by cystostomy (seven cases) has been reported. Hematuria occurred but could be explained adequately in each case by infection, trauma, retention or a combination of these three factors.

CONCLUSIONS

1. Experimental acute urinary retention in the dog causes venous stasis in the bladder with secondary hemorrhage, impairment of function and necrosis. The necrosis leads to rupture of the bladder in from sixty to seventy-two hours.

2. The effect on the kidney appears in about forty-eight hours and consists of hemorrhages into the wall of the pelvis and the interstitium of the kidney with resultant functional impairment.

3. Sudden relief of the retention at any time before the bladder ruptures does not aggravate the lesions but results in recovery.

4. Hematuria may also be produced by infection (cystitis or pyelonephritis) or instrumental trauma.

5. A combination of any or all of these factors suffices to account for the hemorrhages seen after sudden emptying of the bladder.

6. In a small series of patients (ten) treated by me, sudden withdrawal of the retained urine caused no ill effects. The small amount of bleeding is easily explicable as the result of infection or trauma or as the effect of the retention itself.

7. It is unnecessary to assume that sudden emptying of the bladder is responsible for the bleeding which often follows.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.

LOS ANGELES

E. STARR JUDD, M.D.

ROCHESTER, MINN.

JEAN VERBRUGGE, M.D.

ANTWERP, BELGIUM

ALEXANDER B. HEPLER, M.D.

SEATTLE

ROBERT GUTIERREZ, M.D.

NEW YORK

AND

VINCENT J. O'CONOR, M.D.

CHICAGO

PROSTATE GLAND

Resection.—Legueu and Dossot [32] stated that the neck of the bladder is the seat of very diverse lesions all of which end in the same trouble—deficiency of its opening at the time of urination. The rational treatment of this condition is, therefore, destruction or section of the neck and of the relaxed sphincter. Section can be done through the open bladder. When dealing with macroscopic hypertrophy, whether adenoma or carcinoma, the endoscopic route should not be used.

The authors stated that it is illogical to attack a carcinoma of the prostate gland by the urethral route in the hope of opening a passage for urine. This is similar to attempting to treat neoplastic stenosis of the pylorus by destroying the carcinomatous buds with a curet.

The authors further stated that in dealing with microscopic lesions, whether hyperplasia of the neck of the bladder, an inflammatory process, a congenital lesion or a lesion of the nerves, good results can be obtained by endoscopic methods.

Dorman [33] reported that the first 30 transurethral prostatic resections that he performed were carried out without a fatality, except that some patients died later as a result of carcinoma. His thirty-first and thirty-second patients died. He stated that patients who know of transurethral

32. Legueu, Felix, and Dossot, R.: The Endoscopic Treatment of Dysectasis of the Vesical Orifice, Urol. & Cutan. Rev. **37**:32 (Jan.) 1933.

33. Dorman, H. N.: Personal Observations in Prostatic Resection, J. Urol. **29**:361 (April) 1933.

resection choose this operation rather than prostatectomy. Physicians who have had an opportunity to see a transurethral resection properly performed are impressed with the speed and the simplicity of the operation, the lack of danger accompanying it and the astounding immediate results.

Dorman explained the simplicity of the procedure. It is easy for the patient in comparison with prostatectomy. No operation that the urologist is permitted to perform requires more careful attention to a multitude of details, more care and skill in the actual performance of the operation and more meticulous postoperative care than transurethral prostatic resection. The urologist who is fitted by previous training and by temperament to undertake this work can offer his patient something really worth while that the prostatectomist never can duplicate, something that suffering humanity sorely needs and something that will incur the everlasting gratitude of patients.

Ryall and Millin [34] described their prostatic excisor. This instrument differs little from the resectors used in the United States. It has a straight endoscopic sheath, a loop electrode worked by a rack and pinion and a direct vision telescope. Instead of the loop alone moving on the rack-and-pinion mechanism, the telescope and lamp also do so. In this way the loop is visualized with identical illumination and magnification throughout the whole of its excursion. Moreover, almost the whole of the loop is visible, so that during cutting when the lower portion of the loop is embedded in tissue the upper part is clearly seen. The whole procedure is thus visualized. The authors stated that with the armamentarium now available it is feasible to resect as much prostatic tissue as they please. Although agreeing with McCarthy and others that it is often sufficient to gutter the posterior commissural region and establish a shelving floor, they prefer when possible to resect widely, attacking the lateral lobes also. When a very large gland is to be treated, they choose to operate in two stages rather than to subject the patient to a procedure lasting more than forty-five minutes. The indwelling urethral catheter is retained for the five to seven days that elapse between the two stages, as the coagulated area in an imperfectly emptying bladder predisposes to an ascending infection.

Ryall and Millin stated that they found that transurethral resection as applied to malignant growths of the prostate gland, although frequently a most satisfactory procedure, causes more prolonged postoperative discomfort than it does in cases of benign enlargement of the gland. The sloughs take longer to separate. Probably not more than 5 per cent of obstructions of the prostate gland could not be dealt with by transurethral resection, but the authors feel convinced that it is

34. Ryall, E. C., and Millin, Terence: Endoscopic Resection of the Prostate: A Survey, Urol. & Cutan. Rev. **37**:52 (Jan.) 1933.

undesirable to apply the procedure in more than 75 per cent of the cases. In early cases it is probably of great prophylactic value. In the advanced "bad risk" case, in which prostatectomy is contraindicated even after prolonged drainage, transurethral resection has a very definite place. As the authors stated, resection in two stages may be indicated in cases of very large obstructions in the gland, and it is their practice to employ a temporary suprapubic tube in some cases of this type in which infection in the urinary tract might well tip the scale. For relatively young men who have considerable enlargement of the prostate gland and whose cardiovascular and renal function is good, Ryall and Millin prefer suprapubic enucleation unless this is otherwise contraindicated. The expectation of life of such a patient is usually reasonably long, and the rapid development of the hyperplastic process suggests "exuberance": therefore a recurrence may develop within a short time after resection.

Ryall and Millin almost invariably employ a "low spinal anesthesia." From 6 to 10 cc. of 1 : 500 nupercaine in 0.015 per cent saline solution warmed to body temperature and introduced intrathecally gives excellent analgesia of sufficient duration for any form of resection. In their experience, sacral analgesia is less reliable and its administration is no less unpleasant for the patient. They have carried out transurethral resection on 73 patients with but a single death, and in that case there was a malignant growth. Excluding 6 cases of malignant growth, 67 benign enlarged glands were resected without causing a death. There was no selection of cases, and in no case was resection refused. The ages of the patients varied from 54 to 88, and in some instances the blood urea content was as high as 136 mg. in each 100 cc. after drainage for three months. In only 3 cases was cystotomy necessary subsequently. These 3 accidents occurred in the first 13 cases, when the authors were working with a varying technic. Since then resection has been carried out in 60 cases without an unfortunate incident.

The authors concluded that endoscopic resection of the prostate gland deserves a definite place in urologic surgery. It calls for the highest degree of technical skill and if carelessly used may lead to disaster of the greatest magnitude.

Luys,[35] of France, stated that since the discovery of electrocoagulation and of its practical application in the field of urology, he has at last been able to establish the operation which he calls "forage of the prostate" and to make it both practical and completely effective. This operation consists of hollowing out a channel through the hypertrophied prostate gland by way of the natural passages and by means of electro-

35. Luys, Georges: The Endoscopic Surgery of the Vesical Orifice, Urol. & Cutan. Rev. **37**:34 (Jan.) 1933.

coagulation under direct vision. A tunnel is formed to permit a free outlet for urine by the removal of all obstacles which interfere with urination. From this definition it is evident at once that forage of the prostate gland is a much more extensive intervention, and much more radical and complete, than simple endoscopic resection. It destroys all the obstacles which obstruct urination, whether situated at the vesical orifice or in the prostatic urethra. It levels all prostatic protuberances and furnishes an absolutely straight canal, through which not only do sounds pass easily but the patient is able spontaneously to urinate and empty the bladder.

The author stated that various other methods described by different urologists have the same principal fault; namely, they are incomplete. First, because they attack only the vesical orifice, they are unable to destroy the prostatic obstruction totally, and second, because they apply the destructive agent, which is electric heat, under water, they diminish its power of action considerably. Luys' so-called forage of the prostate gland destroys all prostatic obstructions and has a thermic destructive action infinitely more powerful than that of other methods because it operates in a dry field without the intervention of water.

Forage of the prostate gland consists of repeated coagulation of sections of the obstructing gland at repeated sittings, the manner of application being similar to simple fulguration of a vesical tumor. The burned area is then left to slough out. A warning was given to beware of hemorrhage. Luys concluded that forage of the prostate gland, properly performed, gives perfect and lasting results, and that the operative mortality may be regarded as zero.

Joseph [36] stated that transurethral resection of the prostate gland still hides a considerable amount of danger, the mortality not being notably less than that resulting from the now technically perfected operation of prostatectomy. Therefore, he cannot make up his mind to employ to any great extent the instruments constructed in the United States for diminishing the size of the prostate gland, as he considers the danger of bleeding and sepsis, especially perforation, to be just as great as the danger involved in a modern prostatectomy. If the patient on account of advanced age and poor general condition appears unsuitable for prostatectomy, Joseph recommends either permanent suprapubic drainage or vasectomy.

[COMPILERS' NOTE.—Joseph's remarks reflect the opinion of a group of continental surgeons who were prominent from twenty to thirty years ago. Their former indifferent opinion of the skill and technic of

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36. Joseph, Eugene: The Present Position of Endoscopic Operations in Prostatic Hypertrophy and Prostatic Atrophy, Urol. & Cutan. Rev. **37**:59 (Jan.) 1933.

American surgeons has been greatly altered in the last ten years. Unquestionably, the reports of cases of transurethral prostatic resection, if read by Joseph, deserve a more favorable review. Transurethral resection of the prostate gland is practiced in London to a certain extent, and the instruments are modeled after those used in this country. The operation is practically not done in continental countries. In the various discussions at the recent International Urological Congress, the operation was favorably commented on by English surgeons but either was not discussed or was commented on unfavorably by the urologists of France and Germany.]

Bumpus [37] stated that prostatectomy has been performed at the Mayo Clinic only 3 times since August, 1932. In the same period approximately 250 patients were treated transurethrally. This new method of treating prostatic obstruction has increased the work in this field to such an extent that more patients with prostatic obstruction were treated during 1932 than in any other year of the clinic's history, and of the 276 patients on whom transurethral resection was performed none died. The decrease in mortality among aged patients is most gratifying, as is also the short period of convalescence, which is usually about one week in the hospital.

In addition to shortening the postoperative course of the disease, this method has diminished the time required for preoperative preparation. It has long been the belief that preliminary drainage of the bladder can improve a patient's condition only if marked renal impairment secondary to obstruction has occurred or if considerable urinary infection is present. If these two conditions are absent, it does not seem logical that preoperative drainage can be of any service; in fact, such drainage may result in a much poorer surgical risk, for when undertaken in the absence of infection it often has produced infection. Therefore, 44 per cent of the patients were operated on immediately after the diagnosis was made, and the satisfactory postoperative course demonstrated that this departure from a long established precedent was justified.

Bumpus stated that in almost all of 499 cases in which this procedure was used in the last six years, there was residual urine before operation, in large amounts in some instances. After operation, on the other hand, more than 300 patients had no residual urine; 40 had from 1 to 30 cc.; 20 had from 30 to 60 cc., and very few had more than 60 cc. In this group there were 7 deaths—a mortality of 1.4 per cent. Two hundred and ninety-one consecutive patients were operated on without any deaths. Some doubt has been expressed as to the permanence of this form of treatment. Among this group of 499 patients the condition has

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37. Bumpus, H. C., Jr.: Transurethral Surgery, Proc. Staff Meet., Mayo Clin. **8**:204 (April 5) 1933.

been known to recur 11 times. Two patients were relieved by subsequent prostatectomy, and 9 underwent resection a second time. Even in repetition this procedure seems preferable to prostatectomy.

Bumpus expressed the belief that the instrument developed by him, a tubular knife with which the tissue is excised, gives better results than the wire loop electrode which was used on about 50 of these patients. Excision with a cold knife results in much less coagulation of tissue than does excision by means of a high frequency current, and therefore less coagulated tissue is left to act as a secondary source of infection or to produce delayed bleeding by the late breaking away of the scar. Moreover, in his experience, an incised wound heals more rapidly than a cauterized wound. Although bleeding in a more or less severe form was a complication of convalescence in 5 per cent of the cases, it was never a contributory cause of death; it usually can be easily controlled cystoscopically if the patient has not left professional observation.

Bumpus stated that the largest amount of tissue removed so far by this method weighed 63 Gm. Considering the fact that probably not more than a fifth of the hypertrophied gland has to be removed to restore adequate function, the ability to remove this amount of tissue bears testimony to the general applicability of the method. In 575 recent consecutive cases in which prostatectomy was performed, only 32.1 per cent of the removed specimens weighed more than 50 Gm.

Foley [38] discussed the instrument that he uses and his methods of removing obstruction from the neck of the bladder. The sheath and the working elements of his instrument are introduced through the urethra. The tip of the instrument, containing the light, can be turned to a right angle; from the extreme tip a cutting wire passes down to the shaft of the instrument. Traction on this electrode wire bends the deflecting arm of the lamp down to a point at which it illuminates the vesical neck. The cystoscopic field of the telescope gives a mirror image of the object. Several radial incisions are then made into the body of the prostate gland. In making these incisions the electrode conduit is slid down the telescope to a point of sufficient travel to make the necessary cut. The lower end of the cutting element is thus carried down into the urethra and the upper end is projected toward the periphery of the gland, and its length cuts back into the gland. After a number of these radial incisions are made, the instrument is rotated. Rotation of the instrument progresses from one of the radial incisions past the one next to it, so that the block of tissue between the two is completely severed from attachment. By further

38. Foley, F. E. B.: The New Surgery of Bladder Neck Obstruction. Urol. & Cutan. Rev. **37**:17 (Jan.) 1933.

rotation of the instrument in the urethra, the incision is completed. The segments which are removed by this method are usually from four to ten times the size of those removed by other instruments. Foley stated that for dealing with bars, contractures and small hypertrophied glands, the new type punch instruments in ordinary usage at present are entirely satisfactory. In cases of extensive enlargement, the punch type of instrument presents considerable disadvantage. This disadvantage is practically eliminated by the Foley excisor.

Herbst [39] stated that it would be difficult at this time to determine all the indications for electroresection. There is little question but that it will replace operations with punch instruments. In the short period in which it has been used, it can be fairly stated that it is the operation of choice in cases of moderate hypertrophy of the lateral lobe, of hypertrophy of the middle lobe, of formation of median bars and of fibrosis of the neck of the bladder. Whether it will prove to be a practical procedure for the correction of intrusions of the large lateral lobe is a question which only the future can answer. Herbst expressed the belief that it is a fair assumption that men who have become skilled in this method are today using it in at least 75 per cent of cases of urinary obstruction caused by the prostate gland.

Winsbury-White [40] contended that transurethral resection of the prostate gland will not replace prostatectomy and that its use should be limited to cases of fibrous obstruction.

Perineal prostatectomy has had little vogue in Great Britain, largely because the exponents of the suprapubic operations have had no experience with it and because of the unwarranted fear of postoperative urinary incontinence. This can be obviated by proper technic. White described the method that he employed in 40 of 60 perineal operations to avoid this complication. The important features of the technic are preliminary suprapubic cystostomy with preservation of the prostatic capsule to be sutured over the reconstructed urethra and anastomosis of the stump of the divided urethra to the neck of the bladder; the resutured prostatic capsule is secured firmly to the perineal muscles lying superficial to the compressor urethrae muscle in order to provide support for the new posterior portion of the urethra and the readjusted vesical base. In this way the prostatic space is obliterated and large scars are avoided.

Winsbury-White has devised several instruments to facilitate this procedure. He uses for drainage in suprapubic cystostomy an indwelling catheter and a perineal tube which does not enter the bladder.

39. Herbst, R. H.: Electro Resection of the Prostate Gland, Urol. & Cutan. Rev. **37**:64 (Jan.) 1933.

40. Winsbury-White, H. P.: Perineal Prostatectomy, Brit. J. Urol. **5**:113 (June) 1933.

Secondary hemorrhage is rare. In 2 cases it was necessary to remove a few sutures and to wash the clots through the perineum. Recto-urethral fistulas occurred twice and were avoided in 2 other cases by performing suprapubic enucleation after the rectum was opened but before the opening of the urethra..

The author prefers prostatectomy in two stages to suprapubic prostatectomy, with which he has had considerable experience, because it is easier to stop hemorrhage, there is less operative shock, complications due to infection are fewer and convalescence is smoother and less eventful.

Day [41] stated that transurethral resection is here to stay. With continued and increased experience, and with perfection of instruments and of technic, some of the major worries and fears have been largely overcome, and dangers and deficiencies have in a measure been brought under control if discretion is observed. The author stated, however, that in huge adenomatous prostate glands, resection is both unsatisfactory and needlessly dangerous.

Chetwood [42] expressed the opinion that endo-urethral resection of the prostate gland in accordance with the modern technic is a valuable and efficient procedure in many cases of obstructing prostate gland. He stated that the types of obstruction for which this technic is best suited are the fibrous or fibro-adenomatous enlargements of the gland and the bar and lobe formations of minor degree, removal of which can be completed without too great destruction of tissue or too long an operation. The open operation of prostatectomy is best suited to some cases of prostatic obstruction, particularly those with pronounced lobular, bilateral and median enlargement of the gland; in these cases, with proper preparation the skilled operator attains a low degree of mortality and a promise of a permanent and satisfactory end-result. The combined operation of suprapubic incision and removal of tissue by a diathermic excisor may be appropriately applied in cases in which direct vision and drainage are important factors.

Davis and Owens [43] stated that transurethral resection of the prostate gland, properly employed in selected cases, is undoubtedly a valuable procedure. The majority of surgeons believe that this operation will partially replace, but not supplant, prostatectomy. The immediate results of transurethral resection in selected cases seem to be satisfactory. The ultimate results can be determined only by time. The chief advantage

41. Day, R. V.: Transurethral Resection of the Prostate, Urol. & Cutan. Rev. **37**:50 (Jan.) 1933.

42. Chetwood, C. H.: The Obstructing Prostate, Urol. & Cutan. Rev. **37**:44 (Jan.) 1933.

43. Davis, Edwin, and Owens, C. A.: Prostatectomy and Transurethral Prostatic Resection Compared, Nebraska M. J. **18**:41 (Feb.) 1933.

offered to the patient by the transurethral method is a decreased period of hospitalization. Preliminary drainage, however, is just as essential as before prostatectomy. It seems doubtful to the authors whether, in the last analysis, considering the mortality rate and the immediate and the ultimate functional results, the transurethral method offers the patient as great a degree of assurance of continued health and comfort as does perineal prostatectomy.

Lewis and Carroll [44] gave a timely warning against too great enthusiasm for transurethral resection of the prostate gland. They stated that from reports of the experience of capable operators in various parts of the country it may be deduced that it is not only erroneous but dangerously misleading to teach that resection is a "minor" operation. At present, it has not reached a state of perfection that justifies the assertion that it will supplant prostatectomy. It is the responsibility of the operator to draw the line of demarcation between the patients that are fit and those that are unfit for undergoing resection, maintaining an open mind to the advantages and the disadvantages, as well as the appropriateness, of each operative method.

Caulk,[45] after a careful scrutiny lasting over a period of twelve years, stated that he was convinced from his observation of the cases in which operation was performed with punch instruments that transurethral resection can be effectively employed for the removal of at least 80 per cent of all prostatic growths, benign or malignant, and that it can be used for the removal of growths of immense dimensions. He stated, however, that in the case of very large growths, if the patient presents a good surgical risk it is wiser to remove the growth surgically, since it requires more time to relieve the obstruction by transurethral means. If the patient is young and in good condition, the chance of a fatal result of prostatectomy is slight; but old patients present a poor surgical risk, and if time is not to be considered the transurethral method is the operation of choice. It must be performed by repeated operations rather than by extensive removal at any one time.

For years Caulk has pleaded for simplicity in transurethral operation and has advocated multiple stages; in cases in which instrumentation is short, the absorptive surface is slight, the chance of hemorrhage is minimized and the danger of complications resulting from anesthesia is practically eradicated. Extensive and prolonged transurethral operations on the prostate gland are menacing the lives of patients today more than well conducted prostatectomy has for years, and unless

44. Lewis, Bransford, and Carroll, Grayson: Prostatic Resection—Without the Moonlight and Roses, Urol. & Cutan. Rev. **37**:1 (Jan.) 1933.

45. Caulk, J. R.: The Present Status of Transurethral Surgery for the Removal of the Obstructing Prostate, Urol. & Cutan. Rev. **37**:14 (Jan.) 1933.

urologists realize the seriousness of such performances, the progress which has been slowly and substantially developing will be shattered. Caulk further stated his conviction that it is not a part of prudence to perform extensive transurethral resection with the type of drainage that can be afforded by the urethral catheter.

Caulk still feels that light searing by means of cauterization is superior to any form of resection with a high frequency current in that it is easily controlled and the depth of burning is entirely understood, and consequently necrosis and secondary hemorrhage are less likely to occur. The greatest testimony to this is that he has seen but 1 or 2 secondary hemorrhages in 800 operations.

Caulk stated that the serious feature of the transurethral method at present is the competitive struggle for supremacy on the part of the different manufacturers of instruments and the placing of such tools in the hands of the incompetent, untrained operator, who is informed that the instrument is almost fool-proof, and that any one can use it without danger. He stated that it must be realized that these operative procedures require the utmost skill and delicacy of technic, that patients need the same preparation that is required for major operations and that no unnecessary chances should be taken either in operating on unprepared patients or in working under the sublime delusion that the electrical instrument will do the job. It must be made equally impressive that the postoperative care of the patients requires the most stringent attention to detail if the ultimate purpose of operation is to be attained.

Levy and Goldstein [46] resected the prostate glands of 19 selected patients. Three died (a mortality rate of 15.7 per cent); 2 of the deaths were due directly to the operation. Ten (52.6 per cent) of the 19 patients had serious complications following the operation; 14 (73.7 per cent) claimed improvement in one form or another, and only 8 (42.1 per cent) stated that they obtained complete relief from symptoms.

The authors stated that in studies made at necropsy in 2 cases it was observed that comparatively little tissue was removed even though many sections were made. Slight scarring was visible after healing had taken place.

Sufficient preoperative care should be given the patients. The average preoperative stay in the hospital was twenty-seven and seven-tenths days, and the average postoperative stay, twenty-one and nine-tenths days. The authors stated that cystoscopy and tests for residual urine should not be carried out until four weeks after the operation; otherwise a true picture will not be obtained.

46. Levy, C. S., and Goldstein, A. E.: Clinical and Postmortem Study of Prostatic Resections, Urol. & Cutan. Rev. **37**:55 (Jan.) 1933.

Stern [17] wrote that his purpose was not to add anything to the argument for or against the method of transurethral resection for operation on the prostate gland; it was rather to direct attention to the legitimate field of application of this method, to advise fitness of the patient as a criterion on which to base a decision to perform resection, to suggest a method for the accomplishment of the operation and, most important, to advise those entering the field concerning the complications and risks.

Lymphatic Structures.—Llorca and Botár [48] made 50 preparations of the prostate glands of human fetuses, new-born infants and children with a view to studying the arrangement of the lymph nodes of the organ. They observed that the lymphatic structures leave the prostate gland at the level of its upper and posterior parts, either following various arteries (anterovesical, prostatic, superior hemorrhoidal) or canals (vas deferens, ureter) or take a route independent of these organs. They terminate in all the ganglions of the bony pelvis, in most of the external iliac ganglions and in the inferior mesenteric ganglions. The prevenous ganglion in front of the bifurcation of the primitive iliac and hypogastric ganglions receives the greater portion of the lymph from the prostate gland. The highest ganglion with which a direct lymphatic connection exists is the lowest left para-aortic ganglion; the lowest one with which there is a connection is the median retrocrural ganglion.

After the lymphatic structures issue from the right and the left part of the prostate gland, they may cross the median line either on the anteroposterior surface of the bladder or on that of the promontory and reach the opposite side. The collecting lymphatic structures of the prostate gland communicate also with those of the rectum.

Clinical findings confirm the anatomic findings when evidence is submitted that the groups of ganglions most commonly invaded by carcinoma of the prostate gland are the hypogastric and the external iliac, after which come the para-aortic. The invasion of the last named ganglions may be direct, by way of the hypogastric and external iliac chains, which is rare, or indirect, by the visceral route through the hemorrhoidal chain, which is the usual route.

The rarity with which carcinoma of the prostate gland invades the inguinal lymph nodes may be due in part to the fact that invasion of these nodes may occur by either of two different routes: by the retrograde route from the external iliac nodes to the inguinal nodes, or by

47. Stern, Maximilian: The Stern Method of Prostatic Resection: "The Improved Resectoscope," Urol. & Cutan. Rev. **37**:7 (Jan.) 1933.

48. Llorca, F. O., and Botár, J.: Collecteurs lymphatiques de la prostate, Ann. d'anat.path. **10**:40 (Jan.) 1933.

extension of infection from the neoplasm to the perineum, the lower part of the rectum and the anterior portion of the urethra, and thence to the inguinal nodes. The great frequency of invasion of the bladder, on the other hand, is well explained by these anatomic researches. The infiltration reaches first the vesicular muscularis and later the mucosa. The authors think that this route is due to the intimate relations between the collecting lymphatic structures of the prostate gland and the muscular layer of the anterior surface of the bladder. They have also proved that these collectors frequently pass into the prevesical ganglions.

The frequent occurrence of metastasis to bone, particularly into the sacrum and the lumbar part of the spinal column, is explained better by lymphatic than by hematogenous transmission. Metastasis to bone may be secondary to the primary involvement of the presacral or of the para-aortic ganglions, which, as has been seen, receive lymph from the prostate gland and also from these bones. Here a retrograde route from the ganglions to the bony region would have to be assumed. All these considerations show the enormous difficulty involved in surgical treatment of carcinoma of the prostate gland.

Diverticulum.—Heitz-Boyer [49] stated that troubles resulting from the formation of diverticula in the prostate gland are always caused by a disproportion between the size of the orifice leading from the diverticulum into the prostatic urethra and the size of the bottom of the diverticulum itself. The variety of planes that the diverticula may occupy makes it indispensable to make three urethrograms (one anteroposterior view and two lateral profiles, one right and one left), thus giving two oblique views; an anteroposterior view alone might leave a diverticulum undiscovered. Since these formations are often multiple, in the form of a bunch of grapes, the failure to discover one of them may render useless all therapeutic attempts.

Congenital diverticula may exist but are rare. Usually these structures are acquired as the result of earlier suppurative prostatitis, often a number of years previously. A small abscess, possibly microscopic and unrecognized, constitutes the first stage. The second stage is a period of latency, lasting for five, ten or even fifteen years, until some secondary infection, perhaps from the urine, is grafted to one of these cavities, producing the third stage, namely, secondary septicemia of prostatic origin, which brings the patient to the physician. The infective agents are usually colon bacilli or enterococci, but may sometimes be staphylococci.

The local symptoms are those of cystitis, but these are accompanied by general disturbances which are often characteristic: phenomena of

49. Heitz-Boyer: Les formations diverticulaires de la prostate, J. d'urol. **36**:49 (July) 1933.

intoxication, a constant sense of fatigue and incapacity for work; in extreme cases, loss of weight, constant fever and the gravest symptoms of septicemia. The diagnosis is made by urethroscopy and urethrography; in addition, rectal palpation may reveal a more or less marked depression at the level of the cavity. For urethroscopy Heitz-Boyer uses a special instrument with a double or even a triple optical system and a double fenestra, which he regards as indispensable.

Treatment is by endoscopic resection with a high frequency cutting current, and the operation is carried out in two stages. It consists of enlarging the orifice and breaking down the partitions that separate the numerous deep ramifications, which are often difficult to destroy. The close proximity of the rectum warns the surgeon not to take any step without the most perfect visualization of the operative field. The final destruction of every honeycomb cavity may not be feasible if the patient rebels against undergoing a second operation. In such cases it may suffice to finish with curettage by cold or warm etincelage, which will disinfect the alveolar mucosa and so accomplish a clinical cure. A catheter must be left in place for at least a week. Care must be taken not to engage the tip in an immoderately enlarged diverticulum. This may be accomplished by using a Guyon sound with double curvature.

[COMPILERS' NOTE.—It is obvious that when a prostatic abscess has ruptured into the urethra the remaining cavity is almost certain to form an acquired type of urethroprostatic diverticulum.

Gutierrez and Lowsley [50] have thoroughly considered the two types of acquired and congenital diverticula which are found in the urethra. They have reported 7 such cases and have reviewed and tabulated 113 cases from the literature. There is no doubt that in cases in which there is persistent disturbance of urinary function and of the genitalia of unrecognized origin, a urethrocystogram will often disclose the presence of a concealed sac or cavity, which when it is of the retentive type represents a true pathologic and surgical entity.]

UROGRAPHY

In the course of one year, 1,216 urograms were made at the Mayo Clinic, of which 734 were made by the intravenous and 482 by the retrograde method, or a ratio of almost 2:1. The proportion of intravenous urograms is probably much larger than that observed in most clinics, and it may be asked whether this is necessary, in view of the expense involved. The clinic has been using neoiopax as the

50. Gutierrez, Robert, and Lowsley, O. S.: Diverticulos de la uretra, Rev. de med. y cir. de la Habana **33**:229 (April) 1928; Chirurgische Behandlung der Harnröhrendivertikel mit Projektion, Verhandl. d. deutsch. Gesellsch. f. Urol. **3**:312, 1929.

medium of choice because of the better visualization that it produces. The price of the drug has been reduced practically one-half. Braasch [51] stated that it was his understanding that another urographic medium is about to be put on the market which is to retail at less than $1 an ampule. Regardless of this, he stated that intravenous urography affords data which can be acquired in no other way and that undoubtedly it prevents a considerable number of unnecessary cystoscopic examinations. On the other hand, there are definite limitations to the diagnostic value of intravenous urograms, which should be clearly understood. The greatest value of the method lies in the demonstration of renal stasis, such as occurs with hydronephrosis. This condition often can be demonstrated much more clearly by intravenous urography. It is also of value in the interpretation of shadows in the region of the kidney and the ureter. In many cases of lithiasis in which intravenous urography is used, cystoscopy is unnecessary, as a complete diagnosis can be established by the former method alone. Often it is used to visualize a normal pelvic outline and to show normal renal function on the opposite side. For a number of purposes, however, such as the determination of the source of hematuria, the localization of tuberculosis and the identification of abdominal tumors, the evidence afforded is distinctly misleading. In fact, in all cases in which pyuria and hematuria are predominant, cystoscopic examination is necessary in order to exclude the bladder as the possible site of origin. In other words, the data obtained by intravenous urography and those furnished by cystoscopy are usually complementary, and the combined use of the two methods permits of greater accuracy than was formerly possible. The value of intravenous urography as a test of renal function should not be overlooked, since it often gives a better idea of differential renal function than does any other test.

Moore [52] stated that in 50 cases in which neoskiodan was employed intravenously for urography, the following advantages were noted: The substance does not cause pain on injection; it produces shadows of excellent density and detail in the urinary tract, and its intravenous administration has produced almost no systemic symptoms. The volume of solution used for injection into adults is small (20 cc.), and the quantity of the substance required is only 7 Gm. The aqueous solution is stable. So far, Moore's experience leads to the impression that neoskiodan more nearly approaches the ideal medium than any other agent developed for urography.

51. Braasch, W. F.: Report of the Section on Urology. Proc. Staff Meet., Mayo Clin. **8:**201 (April 5) 1933.

52. Moore, Thomas D.: Excretion Urography with Neoskiodan, J. Urol. **30:**27 (July) 1933.

Swick [53] presented a recent development for use in urography, sodium ortho-iodohippurate, which has many advantages. It is inexpensive, has no toxic effects and can be administered in a small volume of diluent. A comparatively small quantity of the salt is required for satisfactory urograms. Good results have been obtained by oral administration as well as by intravenous injection.

Scott [54] stated that in the making of pyelograms great pressure of the injected medium does not enlarge the diameter of the ureterographic shadow beyond that of the normally filled ureter. Pyelovenous backflow can occur with the range of pressures ordinarily used in making clinical pyelograms. The form of the renal pelvis and the presence of disease are apparently not factors in producing this phenomenon. Occurring as it does at low pressures, pyelovenous backflow is an adequate explanation of some phenomena occurring in the pathologic physiology of ureteral obstruction and of some reactions occurring in clinical pyelography. Injection into the collecting tubules of the kidney may occur with the pressures used in clinical pyelography. It is independent of pyelovenous backflow and in the pyelogram may readily be distinguished from it and from extravasation.

Hennig and Lechnir [55] demonstrated in vitro and in vivo that thorotrast (a thorium dioxide contrast medium) is precipitated when mixed with urine. In roentgenograms of the cystic kidney, this precipitation forms shadows that have a peculiarly level upper surface. These can be recognized in the roentgenogram when the patient is standing. The authors stated that in their opinion this is the most accurate method for the diagnosis of sacculated kidney.

Sartorius and Viethen [56] made a study of the various substances in use for retrograde pyelography. The complex iodine compounds which are in general use (iopax and other preparations) are entirely satisfactory and permit a painless, nonirritating pyelogram; consequently, they were accepted by these authors as the best contrast mediums for intravenous injection. They also showed that the colloidal thorium dioxide preparation has the same advantage as these various iodine

53. Swick, M.: Excretion Urography by Means of the Intravenous and Oral Administration of Sodium Ortho-Iodohippurate: With Some Physiological Considerations, Surg., Gynec. & Obst. **56**:62 (Jan.) 1933.

54. Scott, D. E.: The Effects of Pressure of Pyelographic Mediums, J. Urol. **30**:39 (July) 1933.

55. Hennig, O., and Lechnir, J.: Spiegelbildung in Sacknieren nach retrograder Pyelographie mit Thorotrast, eine neue Darstellungsweise erweiterer Nieren, Ztschr. f. urol. Chir. **37**:60 (April 22) 1933.

56. Sartorius, F., and Viethen, H.: Klinische und experimentelle Untersuchungen zur Frage der Kontrastmittelwahl bei der retrograden Pyelographie insbesondere über die Verwendbarkeit des Thorotrastes, Ztschr. f. urol. Chir. **36**:312 (March 11) 1933.

preparations; moreover, it may be used in weaker dilutions and is therefore less expensive. It has the disadvantage, however, as has been shown on several occasions, of becoming stored in the kidney and causing trouble. This rarely happens when only slight pressure is used, but in occasional cases of extensive disease it may cause trouble.

Sporl,[57] in accounting for the dangers usually thought to be associated with the introduction of gas into the renal pelvis and the bladder, made an investigation of this procedure. He stated that it is of value in certain cases and that if a correct technic is used the introduction of gas into the renal pelvis and the bladder is comparatively harmless. He advised the following precautions: (1) substitution of oxygen for air; (2) careful control of pressure and fractional injection; (3) limitation of the amount of oxygen introduced into the bladder to 150 cc., and (4) avoidance of the use of this measure for patients who have cardiac or pulmonary disturbances.

Verrière [58] carried out experiments to discover what would become of a foreign substance (in this instance, 5 per cent india ink in the physiologic serum) injected into the renal pelvis and left in place for a certain time, with the ureter tied, during which the animal resumed its normal life. The lower end of the ureter in some cases served as the point of entrance; in others, the ink was carried directly into the pelvis or into the extremity of the urinary conduit; care was taken to avoid infection, pyelovenous reflux and excessive loss of blood.

After from half an hour to twelve days, india ink was discovered in 13 of 15 animals within the cells of the mucosa, chiefly on the papilla and at its base, and even in the uriniferous tubules. This phenomenon began half an hour after injection, attained its maximum in six hours and then progressively disappeared. In 11 cases the substance was found in the collecting tubules, and in 10, in the cells of the intermediary tubules. It could also be recognized in the venous system and in the interstitial perivascular, peritubular and peripyelic connective tissue. Evidences of it were observed too in the capsule, the lumbar wall and the ganglions. In six experiments carried out under special conditions, similar phenomena were observed in the convoluted tubules.

An attempt was then made to learn whether identical results would be obtained in hydronephrotic kidneys under the same conditions. The small number of experiments (three) makes final judgment impossible. One case had to be ruled out on account of faulty technic. In another case, in which infection was marked, there was no phenomenon except

57. Sporl, H. J.: Ueber die Zulässigkeit der Gasfüllung des Nierenbeckens und der Blase, Ztschr. f. urol. Chir. **36**:404 (March 11) 1933.

58. Verrière, Pierre: Contribution à l'étude de l'absorption intrarénale, J. d'urol. **36**:27 (July) 1933.

ascent of the ink up to the capsule in the tubules in the cortical region; in the third case, only a small number of foreign elements were found in the cells, except at the level of the pyelic mucosa, in which the picture was much like that seen in the first series. Neither rupture nor infiltration was observed, but only a minimal ascent at the level of the papilla in the tubules on the *right side*. In the vessels, in the perirenal region and on the lumbar wall, the conditions were like those observed in the earlier series of experiments.

In a third series of experiments, made for the purpose of discovering lymphatic routes of absorption, milk was injected on account of its fatty content. The results were striking: The fatty elements were found in the same distribution that was observed in the other series, but they were present in far greater quantity and had been carried to higher segments.

Verrière regarded it legitimate to assume that these foreign elements recognized in the blood, in the interstitial tissues of the kidney and in the lymphatic channels arrived there through absorption, passing through the cells bordering the cavities in which they had been placed. Once having entered the cells, the foreign elements evolve in the protoplasm; from the apical pole they reach the other pole, and following along the nucleus they clear the basal membrane and fall into the interstitial tissue, where they are seen gliding along the tubules and vessels.

These experiments are of practical interest in that they suggest that certain painful disturbances following pyelography with irritating substances (renal infections, abscesses of the kidney and even perinephritic abscesses) may owe their origin to this simple fact of absorption—in such cases, that of bacteria crowded into a ureter under the force of vesical contractions. The experiments also suggest that this power of absorption in the walls of the upper uriniferous elements might be utilized therapeutically.

URETHRA

Tumor.—Campbell [59] reported 2 cases of diverticulum of the urethra in boys. In each case urethral stricture existed. In the first case the sacculation followed crushing of the pelvis; in the second, Campbell believed that it followed severe trauma caused by dilation of a urethral stricture at the age of 22 months. Both cases serve to illustrate the importance of urologic examination among young persons, and indicate further that children are heirs to almost every urologic lesion that is associated with adult life.

Rupture.—Haines [60] stated that conservative treatment, such as simple cystostomy, especially in the hands of less experienced surgeons, is

59. Campbell, M. F.: Diverticula of the Urethra, J. Urol. **30**:113 (July) 1933.
60. Haines, Carlyle: Traumatic Rupture of the Urethra, J. Urol. **29**:285 (March) 1933.

a more satisfactory method of treating patients with incomplete or complete rupture of the urethra, whether in the bulbous portion or in the area posterior to it, than the more radical treatment, such as perineal section or urethral anastomosis, which so many advocate. He believes that each case is a law unto itself. No 2 patients will have identical injuries, nor will any 2 suffer the same amount of shock or have the same ability to combat it. Whether drainage by catheter, suprapubic cystotomy, perineal section, end-to-end anastomosis or a combination of all four is relied on depends entirely on the individual case, the length of time following the injury and its severity. The condition of the patient should be the guiding factor in the choice of a method of treatment.

PENIS

Tumor.—A review of 540 cases of carcinoma observed at the Siriraj Hospital, Bangkok, Siam, from 1927 to 1931 [61] showed that 52 (9.6 per cent) of the patients had carcinoma of the penis. If only the cases in men are considered, the percentage of incidence becomes 22.5. This confirms the impression of the relatively high frequency of this disease in the East.

Statistics show the complete immunity of orthodox Jews and the relative immunity of Mohammedans. This indicates that phimosis is the chief predisposing factor and that circumcision performed at birth should prevent carcinoma of the penis. Among the Siamese who are Buddhists, circumcision is not performed unless there is a definite surgical indication, and in the remote areas of that country this operation is practically never performed in childhood.

The average age of the 52 patients was 49.6 years. Half of the patients were farmers who lived in a very primitive way with poor hygienic surroundings. Their clothing was constantly wet and soiled with mud during long hours of work in the rice fields.

Phimosis was definitely present before the onset of the carcinoma in 24 cases; in 26 cases the records did not indicate clearly whether phimosis was present, and in 2 cases there was no phimosis. The Wassermann reaction was positive in 14 of 44 cases. These facts indicate that phimosis and syphilis may have a distinct bearing on the etiology of the disease.

In the 51 cases in which operation was performed, complete amputation of the penis was done in 6, complete amputation with block dissection of the lymph nodes in 8, partial amputation in 17 and partial amputation with block dissection of the lymph nodes in 20.

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61. Noble, T. P.: Carcinoma of the Penis in Siam, Brit. J. Urol. **5**:242 (Sept.) 1933.

When complete amputation was done the inguinal nodes were removed two weeks later. In cases of partial amputation these glands were removed at the time of operation. On histologic examination few of the nodes revealed metastasis, although most of them were enlarged. There was no operative mortality. The end-results are not given.

EPIDIDYMIS, SEMINAL VESICLE AND TESTIS

Cyst of Epididymis.—Patch [62] reported a case in which there was an intravaginal pedunculated cyst of the epididymis with torsion of the pedicle. The symptoms resembled those of torsion of the spermatic cord. At operation, in addition to a large hydrocele there was found within the vaginal sac a gangrenous cyst with a twisted pedicle which was attached to the head of the epididymis. There was a normal sessile hydatid of Morgagni. There were also incomplete descent of the testis and an inguinal hernia.

Patch considered the possible origin of this cyst. The vestigial structures associated with the testis and epididymis are: (1) the appendix testis, or sessile hydatid of Morgagni, a remnant of the müllerian duct attached to the upper pole of the testis or situated in the groove between the testis and the epididymis; (2) the appendix epididymidis, the stalked hydatid from the wolffian body attached to the globus minor; (3) the paradidymis, or organ of Giraldès, a collection of small tubules found above the head of the epididymis and in the lower end of the spermatic cord in front of the vessels; (4) the vasa aberrantia, or ductuli aberrantes, coiled canals with blind ends in the epididymis.

Torsion of the pedicle of any of these structures, especially of the sessile hydatid, may occur. Dix reported 46 cases in which there were symptoms resembling those of torsion of the spermatic cord, although of less severity. The condition usually occurs among patients between the ages of 11 and 14 years and probably is the syndrome often diagnosed as "idiopathic epididymo-orchitis" in children.

Spermatoceles are cysts in communication with the seminiferous system; they may be intravaginal or extravaginal, the latter type being more common.

The cyst under consideration evidently did not arise from either of the hydatids, from the paradidymis or from the superior vas aberrans. It was not openly connected with the seminiferous system, as it did not contain spermatozoa. It may have arisen from the inferior vas aberrans.

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62. Patch, F. S.: Pedunculated Cysts Within the Tunica Vaginalis, with Report of a Case Showing Torsion of the Pedicle, Brit. J. Urol. **5:**122 (June) 1933.

Vasitis.—Wolbarst [63] stated that the evidence that he presented shows that the vas deferens has a definite clinical identity. It may escape infection when infection is present at either end or surrounding it. It may be infected when there is no apparent infection at either end or surrounding it. Moreover, it may be a nidus for pyogenic organisms the presence of which in the vas deferens has not been reported previously. The author stated that influenza and other systemic infections may possibly be a frequent, unrecognized factor in the production of a focal infection in the vas deferens, with resulting stenosis and sterility.

URINARY ANTISEPTICS

Mitchell and Scott [64] studied the effect of urinary acidifiers and antiseptics on 75 patients who had urinary infections; surgical treatment was not indicated, nor had it been given to correct any factor accessory to the infection. The problem of acidification of the urine is important from the standpoint of its effect on infection and in conjunction with the use of methenamine. The criterion of cure was sterile urine on repeated culture. The specimens were obtained under sterile precautions and before breakfast in order to avoid the conflicting effect of a diurnal rise in hydrogen ion concentration. The patients in the first series were observed for four or five days without treatment in order to note the reaction of the urine and the bacterial counts. Various acidifiers were then given to change the p_H toward the acid side. Acid sodium phosphate was given in 20 grain (1.28 Gm.) doses four times a day. In only 1 case was there a downward trend of the p_H, and in none was the bacterial count improved. Acid ammonium phosphate, ammonium benzoate and ammonium chloride given in 20 grain doses four times a day were effective acidifiers, the shift to the acid side reaching a value as low as p_H 4.8 in some cases. To increase the acidity below this point, adventitious acids (ketonic) must make their appearance in the urine. In no case did the change in p_H modify the bacterial count.

Methenamine was then used in 10 grain (0.65 Gm.) doses four times a day in combination with ammonium chloride. In 19 of 50 cases of acute or chronic pyelocystitis cure was complete; that is, cultures were repeatedly negative. A large number of patients were practically cured but refused to cooperate further to complete the cure as it has been defined. Several considered as uncured were improved, as counts well in the millions were reduced to from 4 to 100 organisms per cubic centimeter. Even though the symptoms disappeared, the patients who dis-

63. Wolbarst, A. L.: The Vas Deferens, a Generally Unrecognized Clinical Entity in Urogenital Disease, J. Urol. **29**:405 (April) 1933.

64. Mitchell, D. R., and Scott, J. M.: Studies of Urinary Acidifiers and Antiseptics in Relation to Pyelitis and Cystitis, Brit. J. Urol. **5**:225 (Sept.) 1933.

continued treatment or of whom the authors lost trace were not included among those showing favorable results no matter how sure the progress to a complete cure.

Hexylresorcinol, methenamine and pyridium gave no evidence of having any value as urinary antiseptics.

In studying the failures, the following possibilities were considered: (1) that formaldehyde was not liberated rapidly enough to appear in any quantity at the level of the kidney; (2) that individual strains of organisms were resistant to formaldehyde; (3) that formaldehyde was absorbed by proteins in the urine, and (4) that there was persistence of a focus of infection (colonic absorption). Analysis for formaldehyde of specimens obtained by ureteral catheterization revealed only a slightly reduced amount as compared to that present in vesical specimens obtained simultaneously. This, together with the clinical cures in cases of pyelitis, suggests that methenamine is effective at the level of the kidney.

A definite resistance to formaldehyde was shown to be characteristic of certain strains of organisms, which accounted for the failure in some cases.

Colonic absorption seems to have a place in the etiology and treatment of persisting infections in the urinary tract. In these cases high colonic irrigations, with the administration of Bacillus acidophilus milk by mouth and of urinary antiseptics, were effective.

INFECTION OF URINARY TRACT

Winsbury-White [65] discussed the relation of infections of the genital tract to those of the urinary tract, not only in the lower part of the tract, where the relationship is obvious, but also in the upper part of the tract. In pyelonephritis and in other types of renal infection the possibility that infection of the genital tract is the source must be kept in mind.

Winsbury-White investigated the path by which genital and pelvic infections spread to the urinary tract. India ink, living bacilli of tuberculosis and dead bacilli of tuberculosis were injected hypodermically into the cervix in some cases and into the tissues of the urethra in others. Rabbits, rats and guinea-pigs were used; they were killed from one hour to three weeks after injection. Serial sections were made through the pelvic organs and the soft parts of the posterior pelvic and abdominal walls up to the hilus of the kidney.

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65. Winsbury-White, H. P.: The Spread of Infection from the Uterine Cervix to the Urinary Tract and the Ascent of Infection from the Lower Urinary Tract to the Kidneys, Brit. J. Urol. **5**:249 (Sept.) 1933.

In female animals extensions of infections as a result of injections into the cervix were found in the vesicovaginal septum, in the vesical wall and under the trigon. Extension upward took place through the lymph nodes of the broad ligaments and the posterior wall of the pelvis into the lymphatic structures which lie in such profusion at the level of the hilus of the kidneys, into the fatty areolar tissue in the hilus of the kidney and into the cortex itself. The leukocytic concentration of pigment in the cortex was outside the veins but in the perivascular lymphatic structures.

Injection into the urethral tissues produced the same results. These findings were in contrast to the picture when the infection was descending, with involvement of the glomeruli and capillaries.

Winsbury-White expressed the belief that the great majority of renal infections are ascending, extending from the genitals, the urethra or the vesical trigon along the pathways described, namely, the periurethral areolar tissue and lymphatic structures and the lymphatic structures in the posterior abdominal wall which empty into the lymphatic structures at the hilus of the kidney. He was convinced of this not only because of his injection experiments but because of his clinical experience. The cortex is involved through the lymphatic structures without primary involvement of the renal pelvis.

LESIONS OF GENITO-URINARY TRACT

Counseller [66] reported that in 1932 in the Mayo Clinic 1,186 operations were performed on 972 patients for lesions of the genito-urinary tract. These operations totaled 1,459 surgical procedures. There were 14 deaths—a mortality rate of 1.5 per cent. There were 228 operations on the kidney, 125 on the ureter, 172 on the bladder, 407 on the prostate gland, including transurethral resection, and 527 on the external genitalia. Of the 172 operations on the bladder, 33 were transvesical resections for carcinoma. The various surgical procedures consisted of cystostomy alone, segmental resection and excision, electrocoagulation, insertion of radium and a combination of these, including the use of the cautery. Two of these patients died.

Counseller recently reviewed the results of treatment at the clinic of 600 malignant tumors of the bladder. He found that 165 patients had lived from five to twenty years following various surgical procedures. In previous years electrocoagulation was generally confined to the treatment of infiltrating, highly malignant tumors usually situated at the base of the bladder and considered nonresectable. Seventeen of the 165 patients were treated by this method, and 15 (88 per cent)

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66. Counseller, V. S.: Report of Urologic Surgery for 1932, Proc. Staff Meet., Mayo Clin. 8:207 (April 5) 1933.

were alive and free from vesical symptoms at the time of the report. If these tumors are considered inoperable, the results indicate that the patients who lived less than five years and who were treated by electrocoagulation lived longer and in greater comfort than if such treatment had not been given. Electrocoagulation should, therefore, be considered in the treatment not only of very malignant inoperable lesions, but of those more favorably situated and less malignant. Furthermore, it may be made more effective by combining it with other procedures, such as partial excision of the growth or the insertion of radium. The latter method was used in approximately 50 per cent of the cases in the last year.

Counseller stated that 195 surgical procedures were performed on the kidney. These consisted of pelviolithotomy, nephrolithotomy, nephrostomy, nephrectomy, decapsulation, nephropexy and division and ligation of anomalous renal vessels for hydronephrosis. Four patients died —a mortality rate of 2.7 per cent.

Nephrostomy is being used with increasing frequency as a conservative procedure for temporary drainage of the kidney in cases of multiple renal calculi associated with infection and hydronephrosis. Its temporary use combined with plastic operations on the renal pelvis in cases of hydronephrosis is also advantageous. It has distinct advantages over pelviostomy: The tube can be changed easily, drainage ceases almost immediately following its removal and there is no distortion of the renal pelvis. Nephrostomy was performed in 26 cases as a procedure secondary to pelviolithotomy or nephrolithotomy for multiple renal stones, infection and hydronephrosis and in 2 cases of pyonephrosis in which sufficient renal parenchyma remained to justify a conservative type of operation. Temporary nephrostomy was carried out in a case of pyelonephritis. Nephropexy was performed in 9 cases as an aid to adequate drainage of the renal pelvis. Its use is distinctly indicated following division and ligation of anomalous renal vessels. It was performed in 3 such cases in this series with excellent results. There were no deaths.

Counseller stated that nephrectomy was performed in 95 cases: in 33 cases of unilateral renal tuberculosis; in 24 cases of nephrolithiasis in which the kidney was too severely injured to justify any conservative procedure; in 18 cases of extensive hydronephrosis in which the renal parenchyma was practically destroyed incident to anomalous renal vessels, and in 20 cases of malignant disease of the kidney. There were no deaths in this series.

In reporting the postoperative complications, Counseller stated that of the total group of 972 patients, 69 (7 per cent) had complications but only 1.7 per cent of these died. In 3 patients in whom complications developed, major surgical conditions other than urologic ones were present; these patients were excluded in the calculation of the mortality.

since the urologic procedures were minor and secondary. The total mortality rate, based on the number of patients and not on the number of surgical procedures, was 1.5 per cent.

MacKenzie and Seng [67] made a study of the cause of death in diseases of the genito-urinary tract; their investigation included all the deaths that occurred in the Department of Urology, Royal Victoria Hospital, over a period of fifteen years (265 in more than 11,000 cases). This gives a mortality rate of 2.39 per cent. For the same period, 5,064 major operations were performed, with 187 operative deaths; the operative mortality rate was 3.69 per cent.

The authors concluded that change in the genito-urinary tract of sufficient gravity to be the chief cause of death occurred in less than a third of the cases in the series, that cardiovascular and respiratory changes together were responsible for more than a third of the deaths and that all cardiovascular lesions, perhaps even arteriosclerosis at times, were grave conditions in the presence of serious disease of the genito-urinary tract. They expressed the belief that infection, whatever its source, within the genito-urinary tract or outside it, is a complication of the most serious consequence. The influence of infection, even if mild, on the cardiovascular and respiratory systems in the presence of disease of the genito-urinary tract is so grave as to constitute the "balance of power" between life and death. Almost two thirds of the deaths occurred in surgical conditions of the kidney and prostate gland; prostatism was the single disease entity revealing the greatest number of deaths, though it gave a comparatively low mortality rate.

The authors further concluded that new growths of the urinary bladder cause more than half of the deaths from neoplasms of the genito-urinary organs. The emergency surgical conditions of acute periurethral phlegmon with urethral stricture (extravasation) and rupture of the urethra call for the simplest and the most conservative surgical procedures at first, in order to reduce the high mortality rate.

White [68] stated that in this industrial age and with the vast increase in injuries caused by automobiles, trauma to the bladder and urethra, varying from slight abrasions of the mucosa to complete rupture and destruction of the lower part of the urinary tract, is being observed much more often than formerly. He stated that in general rupture of the urinary bladder is rare. It may be spontaneous, resulting from internal tension or forced injection of fluid or from intense muscular efforts in the presence of obstruction, inflammation or atony. It may

67. MacKenzie, D. W., and Seng, M. I.: Study of Cause of Death in Genito-Urinary Disease, J. Urol. 29:321 (March) 1933.

68. White, E. W.: A Study of Certain Urological Complications Associated with Fractured Pelvis, J. Urol. 29:295 (March) 1933.

be pathologic, caused by the invasion of tumors or by inflammatory processes spreading from organs in the vicinity. According to the recent literature, rupture of the bladder is becoming more common. It is often found in cases of trauma in which the pelvis is fractured. As far back as 1878, Bartels found 65 ruptured bladders in 169 cases of fracture of the pelvis. More recently, Campbell studied 166 cases of fracture of the pelvis at the Bellevue Hospital, New York. In 25 of these (15 per cent) the urethra was also ruptured, and in a number of others there was urinary distress. Campbell reported 55 cases of rupture of the bladder in 20 of which there was a concomitant fracture of the pelvis. In a study of 383 deaths resulting from automobile accidents alone, Bacon and LeCount found 42 cases of fracture of the pelvis, but in only 3 of these was there rupture of the bladder. They estimated that in 0.7 per cent of cases of automobile accidents the bladder is ruptured.

White stated that because of internal hydrostatic pressure rupture of the bladder can in most cases occur only when the bladder contains fluid. The distended bladder has a tendency to lean forward and upward; hence the inferior aspect is elevated and lifted toward the anterior abdominal wall. The base and the lateral and anterior walls are securely protected by the pelvis regardless of the vesical content. Violent force directed to the lower part of the abdomen if the bladder is distended invariably produces intraperitoneal rupture. As the upper portion of the inferior aspect of the bladder is the most movable and at the greatest distance from the point of impact, it is usually the site of rupture. Intraperitoneal ruptures are generally of the bursting type. Extraperitoneal rupture, owing to violent force directed toward the pelvis, takes place into the prevesical space; the surrounding tissues are promptly invaded by extravasated urine and blood, and certain definite objective symptoms are promptly noted.

White stated that the principal symptoms of rupture of the bladder are pain and tenderness over the pubes, vesical tenesmus, distention of the lower part of the abdomen, bloody urine and stoppage of urination; shock and vomiting may or may not be present. If the rupture is intraperitoneal, the pain soon becomes characteristic of intraperitoneal pain, and the usual signs of peritonitis are seen; if the rupture is extraperitoneal, the pain is localized in the lower part of the abdomen, radiating to the perineum and to the legs.

Since the advent of intravenous injections of iopax or neoiopax, the rule has been established that in all cases of suspected injury to the urinary tract intravenous pyelo-ureterograms are made at the earliest possible moment. Injuries to the kidney and ureters are clearly demonstrated if present. The complications likely to arise, whether rupture

of the bladder is extraperitoneal or intraperitoneal, are such that expectant treatment is only rarely justified, perhaps only in incomplete ruptures without evidence of urinary extravasation. In intraperitoneal ruptures, peritonitis and intoxication may be expected in at least half the cases. In extraperitoneal ruptures, extravasation of urine upward may be expected, as the triangular ligament prevents spreading into the perineum. Cellulitis and necrosis usually follow. When a rupture, whether intraperitoneal or extraperitoneal, is diagnosed, immediate operative intervention should be the rule, the first objective being to sidetrack the urine. Suprapubic cystotomy best fulfils all the needs, as it provides adequate drainage and puts the bladder at rest.

White stated that the urethra, like the bladder, may be ruptured by internal pressure, but that rupture is more usually caused by trauma due to blows on the perineum, to crushing of the urethra against the lower surface of the pubic arch or to laceration by spicules of bone from a fractured pelvis. Often, especially in industrial accidents, the rupture of the urethra is caused by what is known as a "straddle fall" on the perineum. The tear in the urethra may be longitudinal or transverse, complete or incomplete, extrapelvic or intrapelvic. In cases of very severe injury, the membranous urethra may be completely torn away from the bladder.

The usual symptoms of a ruptured bulbus urethrae are localized pain, urethral hemorrhage, perineal hematoma and retention of urine. The bleeding is from the meatus, independent of voiding, but when injury is proximal to the external sphincter the blood may remain in the posterior part of the urethra and find its way into the bladder. In intrapelvic rupture there is no perineal tumefaction, but marked ecchymosis usually develops after a time.

White further stated that the diagnosis of rupture of the urethra in the absence of rupture of the bladder presents practically no difficulties. Prompt surgical attack is the treatment of choice instead of costly delay and attempts at instrumentation. He stated the belief that preliminary cystotomy in a case of extensive laceration of the urethra is to be commended; the principle is basically sound.

White stated that until the bladder is opened it is often not possible to distinguish between an extraperitoneal tear of the bladder and an intrapelvic rupture of the urethra. The general guiding rule in diagnosis is that if the bladder is even moderately distended the rupture must be situated below the vesical sphincter. The prognosis of the operative treatment of rupture of the urethra is excellent as regards life but not favorable as regards function. Young reported in detail 9 cases of rupture of the urethra associated with fracture of the pelvis. In these cases the importance of operation was noted, including accurate

repair of the urethra to avoid subsequent complications or death. With early operation, excellent results and absence of complications may be expected in the majority of cases. The postoperative treatment in all cases is important; regular and systematic dilations of the urethra are advised for an extended time, in order to assure good functional results in the future.

Early diagnosis and prompt and intelligent surgical intervention have been of inestimable value in the restoration of life and function in cases of injuries to the pelvis and urethra. Formerly, delay and neglect resulted in irreparable gross advanced pathologic changes, extreme destruction of tissue, osteomyelitis, pelvic cellulitis and gangrene, thrombophlebitis causing septicemia and multiple abscesses.

RELATIONSHIP BETWEEN CYSTIC DISEASE OF THE BREAST AND CARCINOMA

ORWOOD J. CAMPBELL, M.D.

MINNEAPOLIS

INTRODUCTION

Fifty years have passed since Reclus published his classic description of cystic disease of the breast. Since that time much investigative work has been done, and a voluminous literature has developed. However, the practical and important relationship between this disease and carcinoma has never been so decisively established that any one view has been generally accepted. As a result, a wide range of opinion still prevails as to what constitutes its proper treatment. Thus the selection of the surgeon, rather than the nature of the lesion, often determines whether a breast is removed or preserved.

I believe that sufficient evidence is available to justify a more uniform view of this relationship and to evolve a more standardized and conservative policy in the treatment of the disease.

It is proposed to review the literature, to evaluate the information contained in it, to add, together with follow-up information, a series of 290 cases of cystic disease of the breast in which operation was performed, and to draw certain conclusions which will be embodied in the form of recommendations as to the proper management of the disease.

DEFINITION OF TERMS

The many writers who have attempted to embody their various ideas of etiology in the names which they have applied to the disease have cluttered the literature with numerous terms serving no useful purpose and confusing to a reviewer of the subject.

To avoid this confusion, the term "cystic disease" is here used to cover the whole clinical and histologic picture of benign epithelial and connective tissue hyperplasia and degeneration in all their permutations and combinations. While fibro-adenoma is considered by many to be a part of the picture of cystic disease, it is not so included in this article.

In this review of the literature, therefore, the designation "cystic disease" will replace the following commonly encountered terms: Reclus'
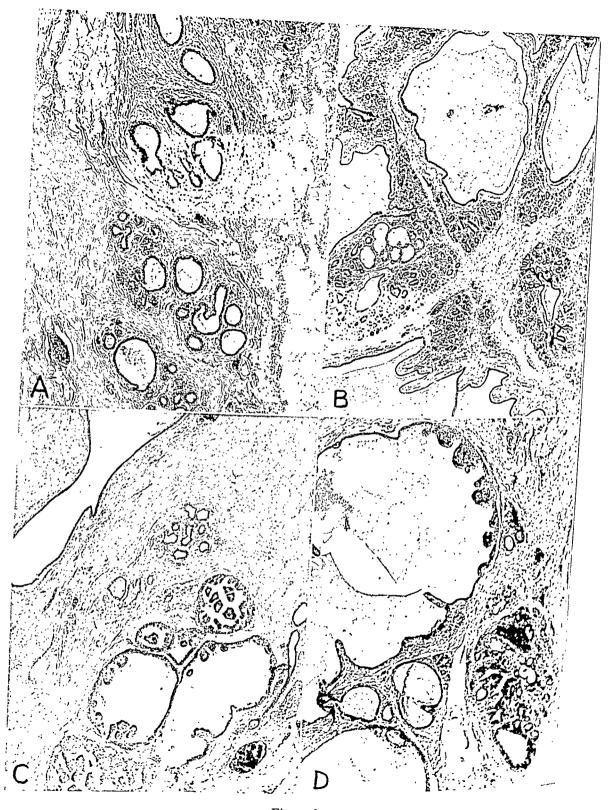
Figure 1

Fig. 1.—*A* (case 95, series I, group A), specimen from a woman aged 30, with simple cystic disease. There were no other masses in either breast. There is simple dilatation of the ducts. No epithelial hyperplasia is seen. The patient was well without recurrence four years after local excision. *B* (case 189, series I, group A), specimen from a woman aged 33, with simple cystic disease. There were no other masses in either breast. The large ducts are greatly dilated and there is some dilatation of the smaller ducts. There is no epithelial hyperplasia. There was no recurrence six years after local excision. The patient had two pregnancies after the operation. *C* (case 17, series II, group A), specimen from a woman aged 43 with simple cystic disease. This shows a group of acini of sweat gland type occurring in simple cystic disease. The presence of this type of glandular structure is not considered in separating the groups into simple and adenocystic types. The patient was well without recurrence three years after simple amputation. *D* (case 2, series I, group B), specimen from a woman aged 36 with sweat gland cystadenoma. There were no other masses in either breast. Cysts lined by acidophil cells are present. Grade I adenocystic disease was found in other parts of the excised tissue. The patient was well without recurrence seven years after local excision.
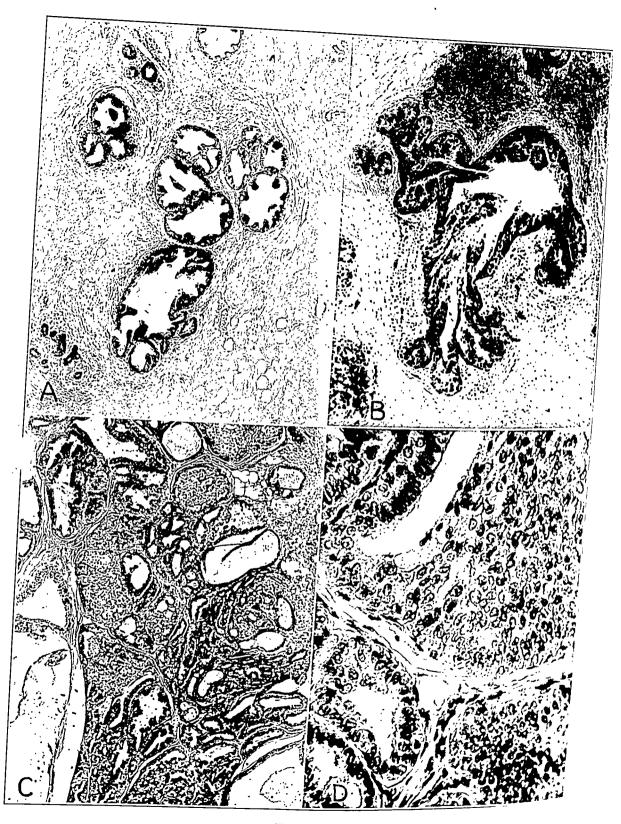
Figure 2

Fig. 2.—*A* (case 22, series I, group B), specimen from a woman aged 37 with adenocystic disease, grade I. There were no other masses in either breast at the time of the operation. Another mass developed in the same breast two years later and was not excised. The patient died five years after the operation from a malignant condition probably originating in the pelvis (see detailed report in the text). The ducts are dilated, and there are papillary ingrowths in their lumens. *B*, specimen from Mrs. M. R., aged 50 (see text for history of case), with adenocystic disease, grade II. She had a brownish discharge from the nipple for one month. A local excision was done in 1926 under the diagnosis of adenocystic disease; there was a recurrence in four months; radical amputation was done elsewhere following a diagnosis of carcinoma; the axillary nodes were not involved. The ducts are solid and there is extension beyond the basement membrane. The patient is living and well six and a half years after the last operation. *C*, specimen from Mrs. N. H., aged 39 (see text for history of case), with adenocystic disease, grade II (border-line tumor). There was a localized mass in each breast. An area of cystic disease had been removed from the left breast five years previously. There was marked epithelial hyperplasia with papillary ingrowths—intracystic papillary cystadenoma. A diagnosis of carcinoma was made from a frozen section, and radical amputation was performed. The axillary nodes were not involved. After study of paraffin sections, the diagnosis was changed to adenocystic disease. The patient is living and well four years after the radical operation. *D*, higher magnification of an area shown in figure 2 *C*.
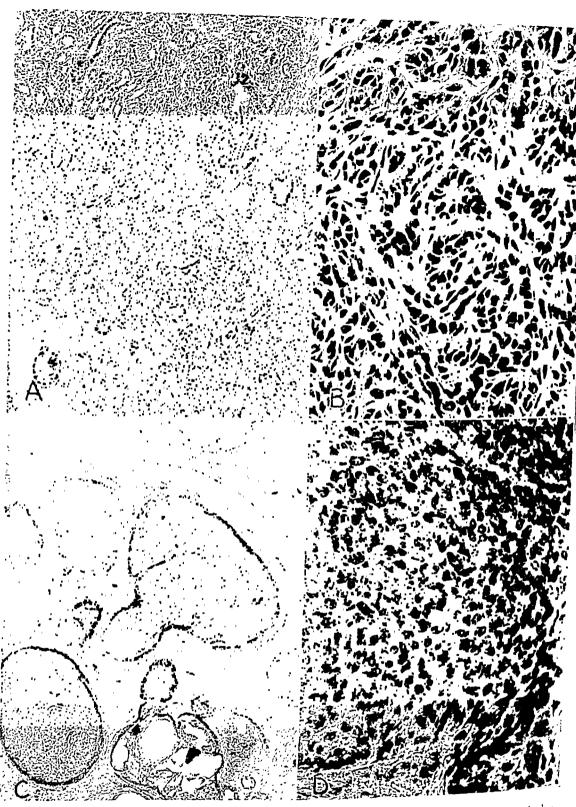
Fig. 3.—*A* (case 10, series I, group C) specimen from a woman aged 21 with adenocystic disease, grade II (border-line tumor). There were no other masses in either breast. Marked epithelial hyperplasia of lobular distribution is seen. The patient is well, without recurrence, three years after the local excision; she has married and has had two pregnancies. *B*, adenocystic disease, grade II. This is a higher magnification of an area shown in *A*. Differentiation from carcinoma is difficult under high magnification. *C* (case 2, series I, group C), specimen from a woman aged 34 with adenocystic disease, grade II (border-line tumor). No other masses were found in either breast. Under low magnification a definite lobular arrangement is noted; the ducts are filled with solid epithelial masses. The patient is well, without recurrence, ten years after local excision. *D*, adenocystic disease, grade II. This is a higher magnification of the section illustrated in *C*.

Fig. 4.—*A* (case 11, series I, group C), specimen from a woman aged 36 with adenocystic disease, grade II (border-line tumor). No other masses were found in either breast. Marked intracystic papillary growth is seen. The patient is well, without recurrence, five years after local excision. *B*, adenocystic disease, grade II. This is a higher magnification of the area shown in *A*. *C* (case 6, series II, group C), specimen from a woman aged 36 with adenocystic disease, grade II. Multiple masses were found in the breast. Adenomatous hyperplasia of lobular distribution is seen. A simple amputation of the opposite breast was performed two years before. The patient is well, without recurrence, eleven years after simple amputation. *D*, adenocystic disease, grade II. This is a high power magnification of the solid alveolar area shown in *C*.

disease, mastitis chronica cystic (König), cystadenoma mammae (Schim-melbusch), abnormal involution (Warren), senile parenchymatous hypertrophy (Bloodgood), épithéliome intra-acineux kystique (Bris-saud), polykystoma épithéliale (Sasse), hydrocystoma mammae (Krom-pecher), lésions scléro-kystiques (Masson) and secondary epithelial hyperplasia (MacCarty).

The term "simple cystic disease" is applied to forms in which epi-thelial activity is limited in degree or altogether absent (fig. 1 *A* and *B*). The term "adenocystic disease," adopted by Bell, is applied to types of the disease in which epithelial hyperplasia forms a prominent part of the picture or entirely dominates it. For the purpose of designating the degree of this hyperplasia, the terms "adenocystic disease, grade I" (fig. 2 *A*), and "adenocystic disease, grade II" (figs. 3 *A*, 3 *C* and 4 *A*), are used.

REVIEW OF THE LITERATURE

It is found convenient to divide the various contributions roughly into groups according to the period and according to the views held concerning the etiology of the disease.

Early Period.—Early writers apparently either took little notice of cysts of the breast or regarded them with complacency.

Cooper and Warren (1837) described single and multiple cysts which they termed "hydatid cysts." They did not, however, confuse them with cysts of true echinococcic origin. These hydatid cysts were regarded as benign and treated by puncture or incision and occasionally by amputation.

Velpeau, in his book on diseases of the breast, also considered cysts benign and recommended nonoperative measures or only the most simple procedures such as puncture, injection of iodine or incision followed by application of an iodine pack to the cyst wall.

Paget, Brodie, Birkett, and Gross described serous cysts and cysts containing papillomas. Both types were regarded as benign, although their occasional association with cancer was noted. Probably, since Gross found that cysts constituted only 2 per cent of his group of tumors of the breast, these men recognized and described only the larger and clinically obvious types. It is to be observed that, while familiar with the microscope and its application to surgical pathology, they still relied mainly on their own clinical experience in the diagnosis of questionable lesions.

In his introduction to "Diseases of the Breast," Velpeau protested bitterly against the use of the microscope as the final arbiter in the diag-nosis of lesions of a doubtful nature. Lesions which experience had shown him to be benign were labeled malignant on histologic study.

With the growing use of, and greater dependence on, the microscope ideas began to change, and much of the security which surgeons had felt in regard to cysts in the breast was lost.

While Billroth did not consider cysts dangerous, he nevertheless included them when he recommended the extirpation of all tumors.

Reclus, whose great contribution to the literature in 1883 was the excellent clinical description which finally established the disease as an entity, found his clinical impression of its benign nature at variance with impressions gained from histologic study. In advising total extirpation of the breasts he was admittedly influenced by Brissaud (1883), who published a detailed description of the histologic character of the disease and who thought it similar to cystadenoma.

Five years later (1888), having observed that his patients remained well, without the advent of malignancy, Reclus wrote that he had returned to his original clinical impression that the process is benign and had ceased doing amputations, except in older women, in whom the danger of cancer is greater.

In a symposium held in Paris in 1888, Brissaud, Trelat, Quenu, Terrier and Terrillon affirmed their faith in the benign nature of cystic disease. Sicre stated that, as a rule, the process is benign, but as he had histologic evidence that it may become malignant, he recommended amputation in older women.

Etiology.—At about the period referred to, interest in the etiology of cystic disease began to take a prominent place in the literature.

In 1892 Schimmelbusch, who occupies much the same position in the German as Reclus does in the French literature, published the results of his thorough clinical and microscopic researches. His cases, demonstrating diffuse and bilateral involvement with the nonencapsulated cystadenomatous type of cystic disease, were considered by him as proof of the neoplastic origin and nature of the process. Bilateral ablation was advised for older women, but recognizing the long chronic course of the disease, and implying an evolution into cancer only in later years, he considered it justifiable to follow a policy of waiting in the treatment of younger women. He was the first to collect a considerable number of cases of cystic disease. In 3 of 45 cases in which an operation was performed, carcinoma was demonstrated microscopically.

Tietze, in 1900, regarded the process as neoplastic. While the lesion must be considered as a primary disease of the epithelium, distinct and apart from carcinoma, the malignant stage is but a short step ahead. Such a transformation occurred in 10 per cent of his cases. Four years later he reported his investigations on senile breasts and concluded that since the epithelial changes typical of cystic disease were found in 25 per cent of older women, the predisposition to malignant tumors in such women was to that degree established.

König expressed his long held view that cystic disease is not neoplastic in origin but is a result of a chronic inflammatory reaction. The cellular infiltration and frequent axillary lymph node hyperplasias were cited as evidence of this explanation. However, König regarded carcinoma as of more frequent occurrence in breasts with the disease than in normal ones.

Delbet (1893) agreed with König. He believed that infection gained access to the breast through the ducts. As added evidence of the inflammatory nature of the disease, he emphasized the important fact that in contrast to true neoplasms, which are disturbing and deforming to the architecture of the organ, cystic disease does not disturb the lobular arrangement of the breast. While agreeing that cancer is more likely to develop in a cystic than in a normal breast, he did not believe amputation to be indicated and preferred to excise the mass locally.

Samelson believed that the evidence favors inflammation as the cause of the disease, but was unable to understand the way and sequence in which the changes were produced.

Syms and Masson, somewhat later, accepted the theory of inflammatory origin. The former believed that the disease is frequently followed by cancer and recommended radical amputation. Masson, who accepted the theory only because it was the most simple, considered that papillary forms are metaplastic and precancerous. Metaplasia, however, does not occur until cysts are formed by inflammatory constriction of the terminal ducts.

Roloff and Sasse occupied a middle ground with respect to the neoplastic or inflammatory origin of cystic disease. According to Roloff, the intimate relationship between connective tissue and epithelium precluded any great activity of the one without a like activity of the other. He likened the formation of cysts to the production of bronchiectasis. In order to be sound, any theory explaining the origin of cancer must, in his opinion, include the factor of irritation.

Lichtenhahn and Saar saw no causal relationship between any inflammatory process and epithelial overgrowth. They believed that cystic disease is a primary epithelial hyperplasia from which cancer is certainly more likely to develop than from normal resting epithelium. The diffuse nature of the process argued against its being considered a real tumor. This characteristic influenced Saar to perform amputations since after simple excisions the remaining mammary tissue always showed the disease even though only microscopically.

According to Theile, the process is neither neoplastic nor inflammatory, but degenerative. From this degeneration, however, neoplastic processes such as fibro-adenoma, sarcoma and papillary cystadenoma may develop. All the stages from the initial formation to the final production of cancer can be demonstrated. Obviously he did not consider

the occurrence of malignant tumors to be very frequent, for he recommended simple excision for localized lesions. For the bilateral, multiple and diffuse processes, in the absence of clinical signs of malignancy, he advised nonoperative measures.

Mintz (1899), Berka and Todyo believed that proliferation of connective tissue is responsible for the production of cysts.

Cornil and Bertels likewise believed that the origin of the disease lies in the connective tissue. The development of cystic changes is aided by stasis, desquamation and, eventually, dilatation. They differed as to the final outcome, the former believing that the process remains benign, and the latter, that the epithelial proliferation continues without any sharp demarcation into cancer.

Robinson believed that there is a causal relationship between the formation of cysts and malignant growth and that cystic disease of the breast should be subjected to radical removal.

Ellis reported a case of cystic disease in which he considered that malignant degeneration had occurred.

Landau thought that cystic breasts were too often amputated because of groundless fear on the part of the patient or physician.

Williams, checking over his experience, was certain that malignant change was less likely to develop in nonmalignant tumors than in normal mammary tissue.

Abbe recommended puncture as a curative measure and Bull advocated puncture followed by excision if the cyst returned.

Sheild and Williams advised puncture or incision with packing in suitable cases. For multiple cysts, multiple puncture or mammectomy was advised.

Stewart criticized Abbe for advocating puncture, since the nature of the fluid is not an index of the character of the pathologic process.

Keibel, Clark and Upcott practiced simple excision, except for diffuse or bilateral lesions, in which case Upcott believed that amputation should be done.

In 1905, Greenough and Hartwell reported their study of 30 cases of cystic disease. Since carcinoma was found in 3 cases, they concluded that the subcutaneous removal of the entire breast was indicated.

In 1907, Greenough and Simmons found an incidence of 15 per cent of carcinoma in 20 cases of papillary cystadenoma. In this special form of the disease they recommended the complete removal of the process. In some cases this could be accomplished by local excision, while in others it required amputation.

The Sweat Gland Adenomas.—The presence in the breast of glands which resemble certain large sweat glands normally found in the axilla, on the sides of the face, in the groins, on the labia majora and around the

anus attracted considerable interest and speculation regarding their relationship to the pathologic process. These glands in the breast, with large, faintly-staining eosinophilic cells often lying on a layer of smooth muscle, the "myo-epithelium," were first described by Creighton, who regarded them as the source of all forms of mammary tumors, including cysts. He believed that they represented a "reversion" to a common embryologic order.

Krompecher referred to these sweat gland types as composed of *Blassen* epithelium and related them to normal types of sweat glands found elsewhere in the body. In the breast they were considered as reversions or atavistic changes. While the proliferation of these cells lags behind that of cylindric epithelium and rarely dominates the picture, they nevertheless take a prominent part in carcinomatous proliferation, in which they transform themselves into polymorphous epithelial cells occurring in sheets.

Herzenberg supported Krompecher's views on the origin of these glands, but found it impossible to satisfy herself that cysts develop through metaplastic transformation as was suggested.

Ewing mentioned cases of carcinoma arising from the sweat gland type of epithelium within the breast.

Masson described the appearance as "metaplasie idrosadenoïde" and believed it to be a true metaplasia rather than an inclusion or defective development.

Corsy agreed with Masson, the appearance being explained as a reversion or metaplasia from the more highly developed type of secreting cell. He suggested that these glands may arise on the basis of a disturbed physiologic process and may disappear completely after lactation.

Delbet (1927) pointed out that they are too constant a finding to be explained on the basis of developmental malformation, and, like Corsy, he linked their origin with a physiologic disturbance. Both believed that while carcinoma is more likely to develop in a breast containing the sweat gland type of epithelium than in a normal breast, the likelihood is not great enough to justify their recommending amputation.

According to Peyron, the common origin of the breast and sweat glands is a sufficient explanation for all structural changes.

Goldzieher and Kaldor considered it unnecessary to resort to a theory of metaplasia to explain the presence of these glands, since metabolic disturbances of the acinar epithelium produce changes that are morphologically identical.

A reviewer of these opinions is left with the impression that whatever the origin of these distinctive types of glands and cells is, they are incidental and play no part in the course of cystic disease. They are definitely not precancerous.

Involution and Physiologic Changes.—The possible influence of physiologic stimulus and of senile and presenile involution on the development of cystic disease has long been observed.

Langhans and Billroth demonstrated the manner in which cysts were formed by the breaking down of intervening septums and the fusion of small involuting cysts.

Creighton, in his work on the mammary gland of dogs, commented on the possible effect of the periodic stimulation "evolution" and regression "involution" on the production of a pathologic process within the breast.

According to Stiles, epithelial stimulation is brought about by hormones originating in the pelvis. Nonoperative measures were advised, since the disease was not considered precancerous.

Syms called attention to the variations in the histologic picture depending on the stimulus then acting. Following lactation, a defective process of involution so commonly leaves an appreciable amount of glandular tissue, persisting in the senile breasts, that Berka believed that the absence of such residual lactation acini is a reliable indication that the patient was never pregnant.

In 1917 McFarland, collaborating with Deaver, attributed the presence of all cysts, in all age groups, to senile or presenile involution. In 1922, he elaborated on this theory to include all the forms of cystic disease. He expressed disbelief in the existence of the diffuse cystadenoma of Schimmelbusch, considering it merely one variation of the process of involution in which residual lactation acini appear in various conditions of retrogressive change. Intracystic papillomas were explained as remnants of broken-down septums. He stated that the process is harmless and has no significance with respect to the subsequent development of carcinoma. In 1927, he brought out the fact that there are localized variations in the response to hormonal stimulation. He exonerated fibro-adenoma as well as cystic disease from any responsibility in the production of carcinoma.

The relationship between the ovaries and the various stages of mammary activity had been recognized and referred to, directly or indirectly, by various early writers. The well controlled and scientific work of a few investigators on the specific hormones in relation to the cyclic changes in the normal breast stimulated fresh interest and speculation concerning their possible etiologic association with cystic disease.

Loeb (1917) and his co-workers showed the effect on the breast of corpus luteum and follicular hormone and worked out the cyclic changes in small experimental animals.

Rosenberg was the first to work out the cyclic variations in the human breast and to coordinate them with the cyclic change in the ovaries.

He found that in each premenstruum, coincident with an active corpus luteum, the terminal ducts show budding outgrowths of epithelium. At first these are solid, but later they become vacuolated to form acini. Toward the end of the period the acini begin to degenerate and eventually disappear completely. During this stage the corpus luteum shows hemorrhage and evidences of cessation of function. In the intermenstrual period only the ducts are present.

Ernst substantiated Rosenberg's observations. Dieckmann, on the other hand, while confirming the presence of a cyclic change, failed to find complete regression of lobular structures in the intermenstruum. Lobules disappear only after prolonged amenorrhea. Rosenberg's observations are explained on the basis of the youth of his patients, since the full capacity to form acini is not acquired until the age of 20. Connective tissue, as well as epithelium, participates in the change. The clinical observations of fulness and distention in the premenstruum are explained on the basis of lobular edema and are not, as Rosenberg contended, due to epithelial activity alone.

Moszkowicz, confirming in general the work of his predecessors, was impressed with the similarity between the normal proliferating lobule of the premenstruum and fibro-adenoma. In his opinion there is a causal relationship between menstrual disorders, benign diseases of the breast and, later, carcinoma. Since any mastopathy may result in malignant degeneration, he advises the removal of areas of cystic disease or the treatment of such areas with roentgen rays.

Dietrich explained the beginning of cystic disease as an evolutionary process initiated by hormones but with an atypical proliferative response. The further development is concerned with connective tissue and epithelial hyperplasia, irritation and, eventually, the formation of benign and malignant neoplasm.

Ingleby believes that fibro-adenomas arise from normal or abnormal proliferation followed by incomplete regression. If secretion without absorption occurs, cysts develop. All the variations of cystic disease can be explained on the basis of variations in the amount of epithelial proliferation and degeneration, the quantity of secretion poured into the ducts and the degree of growth and regression of the pericanalicular fibrous tissue.

Clairmont explained cystic disease on the basis of an endocrine disturbance and stated that the lively process of intermittent change makes the breast a favorable site for cancer.

Cheatle (1928), whose works will be reviewed later, said that cystic disease is really a physiologic process which has become pathologic. The views of Corsy and Delbet, that abnormal physiologic stimulation may produce a sweat gland type of epithelium, have already been given.

Orbach and Moriconi advanced the unconvincing hypothesis that cystic disease is produced by a disturbance of endocrine hormones, which is in turn produced by tuberculosis.

Konjetzny believed that in cystic disease he was dealing with pre-senile involution which could often be traced to disturbances affecting the menstrual cycle. Malignant changes were found in from 30 to 50 per cent of his cases. He recommended excision of the tumor mass in young persons, but advised amputation in elderly women and in patients showing diffuse involvement.

Goens-Rosales found a high percentage of active epithelial prolifera-tion in the breasts of women between the ages of 40 and 95 who had died of conditions not originating in, or directly affecting, the breasts. Of 60 patients examined, 30 had cystic changes, 20 of these showing activity of the epithelium. Precancerous changes were found in 7 of the 20.

Borchardt and Jaffe examined both breasts of 100 women over 40 years of age. Microscopic cysts were found in one breast in 90 per cent of these and in both breasts in 70 per cent. The relation to sexual function is apparent. The disease is twice as common in nulliparous women as in women who have borne children. While the incidence of carcinoma is not as high as some place it, these writers believe that radical amputation should be done in all women over 50. In younger women conservative treatment is recommended.

In contrast to Warren, McFarland and others who stated that the entire process of involution is regressive, Oertel showed that, paradoxi-cal as it may seem, structural and functional decline and loss are asso-ciated with proliferation of regressing cells. This occurs in the parenchyma as well as in the stroma, and with such startling frequency in the breast and prostate of elderly persons that if the condition were to be diagnosed as cancerous the majority of these organs would show in one place or another some stage of developing carcinoma. He con-siders these proliferative changes potentially malignant.

According to Joel, degenerated epithelium reacts differently to stim-ulation by ovarian hormone than normal epithelium does. He believed that malignant degeneration is a frequent occurrence in cystic disease. While fibro-adenomas rarely lead to cancers, it is better to remove them. As roentgen rays have a somewhat selective action on intracystic epi-thelium, they may have considerable value in the treatment of cystic disease.

Keynes and Fischer, holding similar views as to the origin of cystic disease, mentioned a constant secretion and absorption in the nonlac-tating glands. Interference with absorption leads to retention, irritation, hyperplasia of epithelial and connective tissue and, eventually, formation of cysts. Fischer found a high percentage of carcinomas in his cases

of cystic disease. While Keynes did not commit himself as to any causal relationship, he expressed the belief that in the present state of knowledge it is better to deal radically with the disease.

It may be pertinent to mention here some experimental work on the relationship of ovarian hormone to tumors of the breast and specifically to cancer.

Loeb, in 1919, and Cori, who repeated Loeb's work in 1927, showed the effect of castration in preventing the development of spontaneous cancers of the breast in a strain of mice which have an established incidence. If the ovarian hormone is withdrawn early in life (under 22 days), before the breast becomes well developed, spontaneous tumors do not occur. If the hormone acts for an intermediate period (from two to four months), the incidence is reduced but not eliminated. If it is allowed to act longer (from six to seven months), the usual incidence, which in Cori's strain was 78.5 per cent, occurs.

In connection with theories explaining cystic disease on the basis of obstruction to the ducts, Harris has performed some interesting experiments. He tied off and inverted the main ducts in the breasts of 7 dogs. In all cases he succeeded in obtaining high degrees of epithelial hyperplasia which, in places, even broke through the basement membrane into the connective tissue. No metastases developed, but Harris called attention to the fact that metastases are slow to occur in cases of carcinoma of the canine breast.

Yamagiwa and Murayama succeeded in producing 23 cases of cancroid tumors by injecting compounds of tar and tar derivatives into the breasts of 188 rabbits. Metastases occurred in only 1 of these; in all the others the tumors spontaneously disappeared.

The Evolution of Cystic Disease.—The literature contains many references to a sequence of events in which simple cystic processes in the breast gradually assume more and more hyperplastic forms, passing imperceptibly into benign and eventually into malignant neoplasms. Theile, Bertels and Dietrich have already been mentioned as expressing this idea.

Cheatle (1930), who has done a large amount of research, chiefly from the histologic standpoint, described such a process of evolution in detail. Beginning with what he termed "desquamative epithelial hyperplasia," in which cysts are formed, the process may pass gradually into stages of benign and finally malignant hyperplasia. The term "neoplasia" was coined to indicate the latter stage. He drew an analogy between this and the stages in the development of experimentally produced tar cancer in the skin of mice (1925). The progress may be arrested in any stage, but according to Cheatle its complete evolution into cancer accounts for 20 per cent of all carcinomas of the breast.

Cutler (1932), who collaborated with Cheatle (1930), supports this view. In his own publications he stated that 20 per cent of carcinomas develop from cystic disease. These authors regard localized nodularity as a significant clinical sign which requires histologic proof of its innocence. Large cysts, while rarely malignant, are better excised. In cases of diffuse distribution or multiple cysts amputation is advisable.

Ewing, who reported pronounced precancerous changes or miniature carcinomas in 50 per cent of breasts excised for cystic disease, believes that many cancers do not represent wholly new growths but are the result of steadily increasing epithelial overgrowth affecting, not embryonal or misplaced tissue, but the normal adult glandular epithelium. In this respect he supports Cheatle's view.

He differs from Cheatle, however, in his statement that carcinomas so arising usually appear early and dominate the picture. When cystic disease has passed a critical period, it tends to maintain a benign course over many years.

Davis followed Cheatle's teachings. He believed that limited operations should be performed on patients under 35 years of age, while in those over 35, amputation is considered to be the safer procedure.

Askanazy (1925) found a definite relationship between cystic disease and carcinoma. This is particularly true in papillomatous cystadenomas in which the genetic relationship can often be proved topographically.

Bartlett considered cystic disease as a clinical entity showing a variety of histologic pictures. It is neither a new growth nor a precancerous lesion. The same picture, minus gross hypertrophy, is seen in normal breasts. Papillomatous cysts, however, show a tendency toward malignant change and should be excised. The inability to differentiate between blue-domed cysts and papillomatous cysts makes it advisable to explore all such lesions. He found 1 case of cancer associated with blue-domed cyst.

At the Mayo Clinic, MacCarty spoke of primary, secondary and tertiary cytoplasia. Primary cytoplasia with regularly layered epithelium corresponds to what I have designated as simple cystic disease, while secondary cytoplasia, showing epithelial hyperplasia with a disturbance in the regular arrangement, corresponds to adenocystic disease. In contrast to secondary cytoplasia in which the epithelium, regardless of its activity, is confined within the limits of the lobules, the tertiary stage shows infiltration of connective tissue and is malignant. No treatment is indicated for the primary type; for the secondary type wide local excision is advisable for patients under 35 and simple amputation for those over 35 years of age.

Irrespective of etiologic considerations, many authors report definite opinions on the debated relationship.

Sistrunk was uncertain of the existence of any such relationship. Radical amputation was never advised unless the clinical signs of malignancy were present or unless the presence of carcinoma had been proved by microscopic examination.

In 1920 Rodman pointed out the frequent occurrence of cancer in cystic disease and advised radical amputation except in young women. Ten years later he receded from the position that cystic disease is precancerous and advised conservative operative measures.

Colucci, making a detailed histologic study, found carcinoma in such a high percentage of cases that he recommended radical amputation in all cases of cystic disease.

Buonsanti was disturbed by the high incidence of precancerous changes revealed by microscopic study of clinically benign types, but made the pertinent statement that only an investigation of the late results shows whether limited intervention or the radical operation is indicated.

According to Morpurgo, 24 per cent of the carcinomas originate from cystic disease. Semb, who divided his cases into two groups, found carcinoma in 24 per cent of the group in which definite hyperplasia existed. For the simple type he recommended no treatment, but for the hyperplastic type and for the patients with a bloody discharge, he urged simple amputation.

A similar division was made by Kilgore (1928). The occurrence of carcinomas in the more productive type of the disease is sufficiently high to warrant amputation.

Hellwig was likewise able to determine from microscopic examination cases in which carcinoma is most likely to develop. In his opinion 90 per cent of the amputations performed are unnecessary mutilations.

Kozhevnikoff subscribed to the opinion that malignant degeneration is fairly frequent, and cited the occurrence of carcinoma in 7.5 per cent of 80 patients with cystic disease whom he had treated. He advised mammectomy in older women. Of 26 patients treated by roentgen rays, a few were permanently relieved of symptoms.

Goldzieher likened the proliferative type of cystic disease to cirrhosis of the liver. Extensive hyperplastic vegetations are not easily distinguished from neoplasms. Both cirrhosis and cystic disease predispose to carcinoma.

The frequency of cystic disease of microscopic proportions in association with clinical or frank carcinoma is commented on and in some cases forms the basis for conclusions concerning a causal relationship.

Billroth, Ewing, MacCarty, Cheatle, Langhans and others have mentioned this frequent association. Fischer found cystic disease in 14 per cent of 151 cases of carcinoma. According to him, the cystic changes in these cases were primary and the carcinoma secondary. Semb found

an incidence of 55 per cent and Junge one of 83 per cent for the association of cystic disease with carcinoma.

The presence of cystic disease around the site of a carcinoma was explained by Keynes as due to an irritation produced by the carcinoma. He quoted Drew who, by cultural methods, demonstrated the presence in cancers of a growth-activating substance capable of strongly stimulating the growth of epithelial and connective tissue.

Fraser studied whole sections of breasts removed for carcinoma. He found a high incidence of a widespread series of changes similar to certain forms of cystic disease and concluded that a local focus of malignant changes develops first and later spreads through the ducts to produce secondary changes. These spreading cells are none the less malignant, although they are confined within the ducts. Only by postulating a primary malignant focus could he explain the definite centrifugal spread of the associated changes which are always most marked near the malignant growth.

Charteris, using the same type of material, arrived at a different conclusion. In an attempt to determine what changes preceded the malignant tumor, he examined 48 whole breasts removed for cancer. All grades of epithelial hyperplasia were found, including solid sheets of cells which in places were breaking through and invading the connective tissue. Most of the changes were in the ducts, and they were present only to a lesser extent in the acini. The process may be localized or may extend diffusely throughout the breast, with breaks in the duct wall in several locations, thus verifying the multicentric origin of cancer. He was convinced that what he observed represents a long series of proliferative changes, in the final stage of which all transitional forms can be seen. While all the forms are rarely present in the same breast, the impression of their essential continuity is obtained.

Thus far in this review, except in the case of the older clinicians, the views and convictions expressed in regard to cystic disease and its relationship to cancer have largely been obtained by a study of histopathology.

An entirely new approach to the problem is offered by Bloodgood. Convinced that most cases of cystic disease never become malignant and that many needless amputations were being done, he practiced limited operations and followed his patients for years to determine the incidence of carcinoma. Thus he obtained a correlation between the various histologic pictures and the clinical course of the disease.

It is of interest that in 1904 Bloodgood, basing his opinion on microscopic criteria only, had concluded that malignant epithelial change occurred in 10 per cent of all cases of cystic disease. In 1906 he wrote that adenocarcinoma was already present in over 50 per cent of patients with the adenocystic variety of the disease whom he had examined.

In 1921, having changed his opinion, he reported his experience with 350 cases of cystic disease, in 128 of which the treatment had been local excision only. A follow-up showed that carcinoma had developed in 3 of these cases, an incidence of about 2 per cent. He concluded that, with the exception of nonencapsulated cystadenoma, or, as it is here termed, adenocystic disease grade II, cystic disease is not a precancerous lesion and cancer is no more likely to develop in a breast so involved than in a normal one.

In 1929 he amended this impression by including diffuse nonencapsulated cystadenoma among the benign lesions. He had recognized this variety of the disease in over 100 patients and treated them without operation. Malignant tumors did not develop in any of them. In the same year he reported his experience with over 300 cases in which blue-domed cyst was treated by local excision. A follow-up over a period of years showed no greater incidence of carcinoma than in women with normal breasts.

Reviewing his locally removed "border-line" tumors in 1931, he found that all of these patients, over whose diagnosis pathologists had disagreed fifteen years before, were living and well or had died of other causes without having shown evidence of cancer.

Bloodgood has therefore concluded from his years of study, combining and correlating microscopic pictures with the clinical course of the disease, that cystic disease is not a precancerous lesion.

Using the same method of investigation, but confining his attention to intracystic papillomatous processes, Hart reported 104 benign and 24 malignant cases. Of the 24 cases of malignant growths, 21 were recognized clinically, 2 were "border-line" cases, and 1 was clinically considered benign. All the patients were treated by the radical operation. Of the 104 with benign growths 38 per cent had radical amputations, 40 per cent simple amputations and 22 per cent simple excisions. Follow-up information was secured on 66. Regardless of the type of operation, all had remained well. Of the group with malignant changes 10 were followed; 7 of these died of cancer in less than five years, and the others died of causes unrelated to the malignant condition. Hart concluded that the malignant cases had been malignant from the beginning and that when the cyst wall is thin and freely movable and the base not infiltrated, the lesion is benign, regardless of the pathologic process of the papilloma.

Johnson found that of 107 cases of isolated cysts of the breast subsequent malignant tumors developed in only 2. Forty-seven cases of chronic mastitis (cystic disease) were followed, in none of which malignant changes developed. He believes that the evidence does not warrant the tendency to remove breasts for comparatively slight and indefinite lesions.

Peck and White followed their cases of benign tumors, 63 of which were examples of localized cystic disease in its various forms. In none of these did carcinoma subsequently develop.

ANALYSIS OF THE LITERATURE; COMMENT

In summarizing and classifying the aforementioned opinions it is found that while a few writers are noncommital, the majority are easily divided into two groups: those who consider cystic disease to be a benign lesion with no causal relationship to cancer, and those who believe it to be precancerous and a menace to the patient. Of those expressing definite views, twenty-three were of the former and forty-two of the latter opinion.

The treatment advised corresponds to, and in the majority of cases is consistent with, the particular view held. There are individual variations and concessions, particularly in dealing with younger women. The etiologic concept of the disease has surprisingly little influence on the molding of opinion regarding the important relationship in question. It is further noted that, with rare exceptions, those who subscribe to the precancerous theory of cystic disease obtained their data and reached their conclusions through histologic methods of research. On the other hand, advocates of the theory of the benign nature of the disease are just as consistently composed of older clinicians who express belief based on their own clinical experience, or those of the newer group who, pursuing the follow-up method of investigation, have subjected their diagnoses and prognoses to the proof of time.

Because of this close correlation one is led to believe that conclusions are practically predetermined by the method of investigation and that it is the method rather than the conclusion which merits critical consideration.

The histologic evidence invoked in favor of the precancerous theory of cystic disease may be briefly summed up:

1. Cystic disease is frequently found in association with frank carcinoma.

2. Various gradations of epithelial proliferation may exist to give the impression that cystic disease represents a progressive evolution of epithelial hyperplasia eventuating in carcinoma.

3. The examination of tissue removed from breasts containing cystic disease frequently reveals histologic pictures which may be interpreted as representing early carcinoma.

It seems established that a high percentage of frank carcinomas show associated changes characteristic of cystic disease of microscopic proportions. It is not established, however, that cystic disease of clinical proportions is frequently encountered under similar conditions. On

examination Charteris found cystic disease of microscopic proportions in the majority of 48 breasts removed for carcinoma. In only 2, however, were the changes of such a degree as to be clinically recognizable.

Recently I reviewed the cases of carcinoma of the breast in which operation was performed at the Minnesota General Hospital between the years 1916 and 1928. Of 88 cases only 4 showed a history of antecedent masses which could have represented cystic disease. In 444 cases of carcinoma Johnson found but 2 in which an antecedent history of cystic disease was obtained.

In view of the extreme prevalence of cystic disease in all age groups (Pribram, Fischer, Goens-Rosales, König, Borchardt and Jaffe, Hahn, Morpurgo and others) the failure of cystic disease to take a more prominent part in the antecedent history of carcinoma of the breast is striking and inconsistent with the supposition of a causal relationship in the occasional cases in which cancer and cystic disease of clinical proportions are found together.

MacCarty indicated the fallacy of such an assumption when he said that the coincidence of benign and malignant hyperplasia does not prove that one necessarily preceded the other.

Theile, Bertels, Dietrich, Cheatle (1930), Cutler (1932), Charteris and others constitute a group which believes in the evolution of many carcinomas through successive stages of the epithelial hyperplasia found in cystic disease. Ewing, himself a supporter of the precancerous theory, named the great weakness in this approach to the problem when he stated that in no case can one trace the evolution of suspected areas into fully developed cancer. However, Junge, Moszkowicz, Goldzieher, Bertels and Charteris believe that they have demonstrated carcinoma arising not only in one focus, but simultaneously in several different foci in the breast.

The opinion as to the multicentric origin of cancer of the breast was severely criticized by McFarland who pointed out that, except for extension by lymphatics and ducts, a carcinoma is in continuity through its whole extent. No one, he affirmed, has ever seen the beginning of a cancer. Fraser explained the escape of epithelial cells from ducts in which they have been confined, not as new foci of malignant change, but as extensions of malignant cells from the primary tumor through the ducts to establish secondary sites of carcinoma in other parts of the gland.

These contradictory interpretations of the same picture illustrate the most fundamental handicap in the use of histologic methods alone in determining the relationship between cystic disease and cancer. The lack of generally accepted diagnostic criteria for the differentiation of benign from malignant hyperplasias has resulted in the widest range

of interpretations and probably explains the high incidence of malignancy in cystic disease reported by Konjetzny (1921), Semb and Morpurgo.

Correlation between the histologic picture of a lesion and its clinical course over a period of years has enabled the diagnoses and prognoses to be made with a high degree of accuracy in the great majority of cases. There are, however, certain so-called "border-line" lesions in which this correlation has not been established. Failure to recognize these lesions or their ready inclusion with malignant growths creates a distorted impression of the nature of cystic disease which is not verified by its clinical behavior as revealed by Bloodgood (1931), Hart, Johnson and others.

I believe that the outlined basic handicaps place a limit on the information which may be obtained by purely histologic methods and that the behavior of a lesion over a period of years rather than its appearance under the microscope is the accurate index in determining its true nature. Therefore our researches should logically be directed along clinicohistologic lines.

SOURCE OF THE MATERIAL

Cases of cystic disease were obtained through the records of the department of pathology at the University of Minnesota, through the Minnesota General Hospital and from six private hospitals in Minneapolis and St. Paul. Only cases in which the original microscopic sections were available or in which the diagnosis had been made by a recognized and competent pathologist were used.

While there is no clearcut division in the degree of hyperplasia manifest in different tissues, in order to determine whether or not those showing the extremes of proliferation merit any special consideration it was thought advisable to subdivide the adenocystic group into cases of grade I and grade II, the latter showing the more marked proliferation.

I graded the cases after having examined the sections of 75 per cent. The other 25 per cent represents cases of which the sections were not available. Accepting the pathologists' diagnoses, the latter cases were distributed as follows: Those bearing only the diagnosis of cystic disease were placed with cases of simple cystic disease and those in which adenocystic disease was specified were placed with the cases of adenocystic disease of grade I. The cases in the adenocystic group of grade II are only those of which I studied the sections myself.

Follow-up information was obtained through the private physician. In many cases, however, information was sought directly from the patients. Since these were, for the most part, women who are naturally concerned about their breasts, it is considered that the information relative to recurrence or to the possible development of malignancy is sufficiently accurate to warrant their inclusion in this material.

PRESENTATION OF MATERIAL

Two series of patients who were followed up are presented: series I, composed of 233 women treated only by local excision, and series II, composed of 57 women treated by simple amputation. Since the two series are used for different purposes, they are commented on separately. In regard to etiologic factors, however, they are considered both separately and in combination.

Of the 233 cases in series I, 82 per cent were graded as simple cystic disease (group A), 12.4 per cent as adenocystic disease grade I (group B) and 5.6 per cent as adenocystic disease grade II (group C).

Of the 57 cases in series II, 73.7 per cent were graded as simple cystic disease (group A), 14 per cent as adenocystic disease grade I (group B) and 12.3 per cent as adenocystic disease grade II (group C).

Of the whole material, composed of 290 cases, 80.3 per cent were graded as simple cystic disease and 19.7 per cent as adenocystic disease.

TABLE 1.—*Age Distribution in Combined Series I and II* *

Group	20 to 24 Years	25 to 29 Years	30 to 34 Years	35 to 39 Years	40 to 44 Years	45 to 49 Years	50 to 54 Years	55 to 59 Years	60 to 65 Years	Total
A	14	18	30	45	54	41	15	3	3	223
B and C	8	4	5	12	7	9	4	3	2	54
Total cases	22	22	35	57	61	50	19	6	5	277
Percentage	8	8	12.6	20.6	22.1	18	6.9	2.1	1.7	100

* In 13 cases no age was reported.

Age.—By combining series I and II and arranging the cases in five year periods according to the age at operation, the maximum incidence (22.1 per cent) is found between the ages of 40 and 45 (table 1). This coincides with the observations of Abbe, Keynes and Bloodgood. Kozhevnikoff, on the other hand, found the maximum incidence to be under 40 years of age.

Considered in distribution by decades, the maximum incidence (40.1 per cent) is within the period from 40 to 50 years. The maximum incidence of carcinoma is within the same period (Bunts, Crile, Evans and Leucutia, Lane-Claypon, Lee, Pfahler and Widmann).

A series of 8,053 cases of carcinoma of the breast reported by Lane-Claypon and arranged in quinquennial periods according to the age at operation is used for comparison with the similarly arranged cases of this series. This comparison is graphically represented in figure 5.

It may be observed that whereas the incidence of cystic disease reaches 8 per cent before the age of 25, reaches a maximum between 40 and 45 and drops quickly after 50, the incidence of carcinoma is almost negligible until after 30, reaches a maximum between 45 and

50 and then (in contrast to cystic disease) drops slowly until advanced ages are reached. The peaks are but five years apart, demonstrating the considerable overlapping in the age distribution for the two diseases.

The theory advanced by Cheatle (1930) and others, that cystic disease starts in its more simple forms early in life and gradually, over a period of years, progresses through gradations of epithelial hyperplasia, meets with strong contradictory evidence when the age distribution for adenocystic forms of the disease is examined. It would seem reasonable, if such a theory were indeed a fact, that the maximum incidence of the adenocystic forms would be found in a higher age group
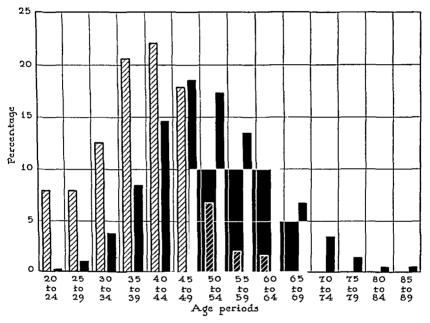
Fig. 5.—Graph showing the comparative age distribution of 290 cases of cystic disease of the breast and 8,053 carcinomas of the breast (Lane-Claypon) arranged in five year periods. The striped areas indicate cystic disease; the black areas, carcinoma.

than that of simple cystic disease. Such is not the case, however, for the maximum incidence of adenocystic disease is between the ages of 35 and 40 in contrast to simple cystic disease, which is most frequently encountered between the ages of 40 and 45. The incidence of 14.8 per cent of all cases of adenocystic disease before the age of 25 and of 22.2 per cent before the age of 30 is incompatible with Cheatle's theory. Figure 3 *A* is a photograph of a section of mammary tissue removed from a girl aged 21, and figure 6 *C* shows a section from a girl 22 years of age. Both reveal degrees of epithelial hyperplasia which, according to the aforementioned theory, should have required years to develop.

Fig. 6.—*A* (case 6, series I, group B), specimen from a woman aged 33 with adenocystic disease, grade I. No other masses were found in either breast. An adenomatous type of hyperplasia is seen. The patient is well, without recurrence, six years after local excision. *B*, adenocystic disease, grade I. This is a high power magnification of the area illustrated in *A*. At this magnification the differentiation from carcinoma is not readily made. *C* (case 1, series I, group C), specimen from a woman aged 22 with adenocystic disease, grade II. No other masses were found in either breast. Adenomatous hyperplasia and cysts, with a definite lobular distribution, are seen. The patient is well, without recurrence, three years after local excision. *D* (case 13, series I, group C), specimen from a woman aged 27 with adenocystic disease, grade II. The distribution in the breast is unknown. Adenomatous hyperplasia in lobular arrangement is seen. The patient is well, without recurrence, two and a half years after local excision.

Duration of Symptoms.—It is found that 35 per cent of all the patients reported for operation within one month, and 68.6 per cent within six months of the beginning of symptoms (table 2). There is no way of noting in what percentage of the cases of longer duration the delay represented a period of observation on the part of the sur-

TABLE 2.—*Duration of Symptoms in the Combined Series* *

| | Months | | | | Years | | | | | | | |
	1	1 to 3	3 to 6	1 to 12	1	2	3	4	5 to 9	10 to 14	Over 15	Total
Group A												
Number......	62	33	32	13	10	8	6	..	7	1	3	175
Percentage....	35.4	18.9	18.3	7.4	5.7	4.6	3.4	..	4.0	0.6	1.7	100.0
Groups B and C												
Number......	14	2	6	5	4	6	2	..	..	2	1	42
Percentage....	33.3	4.8	14.3	11.9	9.5	14.3	4.8	..	..	4.8	2.3	100.0
Total												
Number......	76	35	38	18	14	14	8	..	7	3	4	217
Percentage....	35.0	16.1	17.5	8.3	6.5	6.5	3.7	..	3.2	1.4	1.8	100.0

* In 73 cases no duration was reported.

TABLE 3.—*Marital State in the Combined Series*

	Married	Unmarried	Total
Group A..............................	165	68	233
Group B..............................	28	9	37
Group C..............................	10	10	20
Total..............................	203	87	290

TABLE 4.—*Pregnancies in the Combined Series*

| | Before Operation | | After Operation | |
	Number of Cases of Pregnancy	Total Adequate Histories	Number of Cases of Pregnancy	Total Adequate Histories
Group A.........................	78	162	10	119
Group B.........................	14	26	2	22
Group C.........................	3	13	2	11
Total.........................	95	201	14	152

geon. Of the simple cystic cases, 20 per cent had durations of one year or over, while 35.7 per cent of the adenocystic group had shown symptoms for over one year. Six and three-tenths per cent of the simple cystic group of cases and 7.1 per cent of the adenocystic group had shown symptoms for over five years.

Marital State and Pregnancies.—Of the entire group of patients, 30 per cent were unmarried and presumably had never been pregnant (tables 3 and 4). Of 201 patients with an adequate history 95, or 47 per cent, had been pregnant before operation. Of 152 patients for

whom information on this point was available, 14 have had pregnancies since the operation. Since on the average cystic disease occurs later than the age of woman's greatest fertility, and since of this series, 30 per cent were single women, it is not surprising that there were not more subsequent pregnancies.

Kilgore (1929) showed that the actual incidence of malignant growths occurring during pregnancy is greater than the estimated incidence in any one year. In 12 cases of series I (in which only local
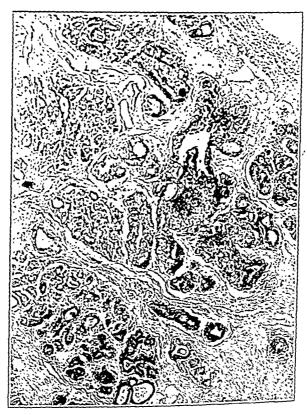
Fig. 7.—(Case 7, series I, group C), specimen from a woman aged 42 with adenocystic disease, grade II. No other masses were found in either breast. Adenomatous hyperplasia with formation of solid lobules is seen. The patient is well, without recurrence, three years after local excision.

excision was performed) the breast has withstood the strongest of all physiologic stimuli without showing development of carcinoma. The patient with a lesion (fig. 3 A) which was diagnosed as adenocystic disease grade II, but which many would have diagnosed as malignant, has had two pregnancies since the local excision of the mass. She has remained free from recurrences or other pathologic changes in the breast.

Pain.—In cystic disease there is little correlation between the degree of pain and the nature and extent of the process (table 5). In this series pain was present in 30.5 per cent of the simple cystic group, in 31.3 per cent of the grade I group and in 33 per cent of the grade II adenocystic group.

Cheatle (1930) and Cutler described its frequent presence in the early changes of "mazoplasia." The latter reported encouraging results in the control of pain by the use of ovarian residue administered orally. He believes that the changes in the breast responsible for the pain were produced by an excessive amount of corpus luteum hormone, and that

TABLE 5.—*Pain* *

	Before	Total Adequate Histories	After	Total Adequate Histories
Group A	53	174	7	233
Group B	10	32	4	37
Group C	5	15	1	20
Total	68	221	12	290

* Six of these patients reported pain both before and after operation.

TABLE 6.—*Discharge*

	Excision Series		Amputation Series		Total	Total Adequate Histories
	Blood	Serous	Bloody	Serous		
Group A	2	2	1	..	3 bloody 2 serous	174
Group B	1	..	1	..	2 bloody	32
Group C	..	..	3	..	3 bloody	16
Total	3	2	5	..	8 bloody 2 serous	222

the administration of ovarian residue counteracts or inhibits this excessive secretion.

From the diagnostic standpoint pain is of little value. Bartlett (1921), Crile and others have found it to be present only in the late stages of carcinoma. Cheatle (1927) reported a case in which the biopsy specimen from a painful area, prior to the appearance of a mass, revealed an early carcinoma. Kozhevnikoff named pain as one of three clinical signs of cystic disease. It was present in 57 per cent of his cases.

In this series, of 55 patients who reported pain prior to operation, 6 had persistence of this symptom. Six who had not noticed pain before reported pain after the operation.

Discharge.—The significance of a discharge from the nipple, particularly of a bloody discharge, has been variously interpreted (table 6). Judd, Miller and Lewis as well as Adair have found about the same

proportion of benign and malignant lesions to be responsible for its presence. Cutler (1932) and Floyd and Haggard thought that in the majority of cases bleeding is due to small benign duct papillomas and rarely to malignancy. Hart, considering only papillary cystadenoma, found that 48 per cent of the benign and 12 per cent of the malignant cases showed discharge as the most prominent symptom. Joel stated that he had never seen malignant degeneration in his cases of bleeding breasts. Knoflach and Urban followed 40 patients with a bloody discharge from the nipple; 30 of these were operated on and 10 were not. In twenty-three years there was only 1 patient of whom they lost track. Carcinoma did not develop in any of the others. MacNeal and Cheatle (1932), on the other hand, regard bleeding as of grave significance. Pribram considers lesions which produce bleeding as intermediate between benign and malignant growths. Bloodgood (1922) and Peck and White did not operate for bleeding alone. Bleeding, according to them, is only a symptom and, occurring without a palpable tumor, does not demand treatment. Hellwig, Hart, and Floyd and Haggard performed local excisions for diagnosis and, failing to find a malignant growth, considered this procedure sufficient. The latter, however, recommended simple amputation for women over 35 and for those who cannot be closely observed after local excision. Knoflach was content with local excision in cases of discrete tumors producing bleeding, but he urged amputation in cases of breasts showing diffuse resistance.

In 1926 Erdheim believed that local excision often sufficed for the treatment of benign lesions producing bleeding. One year later he changed this opinion and recommended radical amputation.

Mintz (1899) was so impressed with the frequency of malignancy in lesions showing a bloody discharge that he performed the radical operation in all such cases.

Cutler (1929) has demonstrated a method of transilluminating the breast to reveal small sources of bleeding which would otherwise defy localization. Fray and Warren advocated stereoscopic roentgenography as an aid to localization and differentiation.

In the present series of 222 cases in which adequate histories were obtained 8 cases showed a bloody and 2 a serous discharge. Five of the 8 patients were treated by simple amputation; 1 of these died of carcinoma of the stomach one year later. The other 3 and the 2 patients with a serous discharge were treated by local excision. All remained free from recurrence, although 3 were subsequently operated on for involvement of the opposite breast.

Antecedent Treatment.—Of the 43 patients who at some previous time had had lesions in the breast, 10 had had local excisions of benign masses (fibro-adenomas and areas of cystic disease) from the same breast and 12 from the opposite breast (table 7). In 1 bilateral local

excision had been performed, and in 2 local excision of one breast had been combined with simple amputation of the other. Seven stated that they had had lactation mastitis or an abscess in the same breast. Seven had undergone a simple, and 1 a radical, amputation for benign lesions. On 3 patients the radical amputation for cancer had been performed.

Distribution of Disease Process.—The distribution of the disease in the breast, as revealed by clinical examination, was, for the sake of convenience, designated as localized, multiple and diffuse (table 8). Any single mass occupying no more than one third of the breast was called

TABLE 7.—*Antecedent Treatment*

| | Excisions for Benign Lesions | | Amputations for Benign Lesion | Amputation for Cancer | Mastitis and Abscesses |
	Same Breast	Opposite Breast			
Group A..........................	12	11	7	3	6
Group B..........................	1	1	..	..	1
Group C..........................	..	..	1	..	..
Total.......................	13	12	8	3	7

TABLE 8.—*Distribution in Relation to Type of Treatment*

| | Localized* | | Multiple | | Diffuse | | Total of Adequate Histories |
	L. E.	S. A.	L. E.	S. A.	L. E.	S. A.	
Group A.......................	139	18	11	8	2	5	183
Group B.......................	23	2	..	2	..	3	30
Group C.......................	9	2	1	1	..	1	14
Total.......................	171	22	12	11	2	9	227
Percentage....................	85.0		10.1		4.9		100

* L. E. indicates local excision; S. A., simple amputation.

localized. The excision of no more than one half of the breast was considered a local excision.

Of 227 patients of whom an adequate description was available, 193 (85 per cent) had localized, 23 (10.1 per cent) had multiple, and 11 (4.9 per cent) had diffuse, distribution. Fourteen of this number had bilateral localized involvement and 1 had bilateral multiple involvement. Seven of the 14 patients with bilateral involvement were treated by local excision in one breast only, and 7 underwent local excision in both breasts. Bilateral simple amputation was performed on the patient with bilateral multiple tumors.

The influence of the distribution of the disease within the breast on the type of treatment administered is indicated by the high percentage of multiple and diffuse processes in the cases of amputation.

Follow-Up Period.—Series I: Two hundred and thirty-three patients were treated by local excision (table 9). The minimum follow-up period was two years, and the maximum, fourteen years.

Of the entire series of cases, 89.2 per cent were followed three or more years, 60.4 per cent were followed five or more years, and 15.9 per cent were followed ten or more years.

Of the 190 cases constituting the simple cystic group (group A), 89.5 per cent were followed three years or more, 62.1 per cent, five years or more, and 16.3 per cent, ten years or more.

TABLE 9.—*Follow-Up by Years*

	2	3	4	5	6	7	8	9	10	11	12	13	14	Total	Percentage
Series I, Patients Treated by Local Excision															
Group A*	20	30	22	25	21	18	9	14	11	6	7	3	4	190	81.9
Group B†	2	8	1	4	4	3	2	1	2	..	2	..	..	29	12.5
Group C	3	5	1	2	..	..	..	..	1	..	1	..	..	13	5.6
Groups B and C	5	13	2	6	4	3	2	1	3	..	3	..	..	42	18.1
Total	25	43	24	31	25	21	11	15	14	6	10	3	4	232	
Percentage	10.8	18.5	10.3	13.4	10.8	9.1	4.7	6.5	6.0	2.6	4.3	1.3	1.7		100.0
Series II, Patients Treated by Simple Amputation															
Group A	1	7	4	5	6	3	4	5	2	3	2	..	..	42	75.0
Group B	1	2	2	..	..	..	..	..	1	1	..	..	..	7	12.5
Group C	..	..	3	2	..	1	..	..	..	1	..	..	..	7	12.5
Groups B and C	1	2	5	2	..	1	..	..	1	2	..	..	..	14	25.0
Total	2	9	9	7	6	4	4	5	3	5	2	..	..	56	
Percentage	3.6	16.1	16.1	12.5	10.7	7.1	7.1	8.9	5.4	8.9	3.6	..	..		100.0
Combined Series															
Number	27	52	33	38	31	25	15	20	17	11	12	3	4	288	

* In one case cancer developed within one year.
† One patient died one year later of carcinoma of the stomach.

Of the 42 cases constituting the adenocystic groups (groups B and C), 88.1 per cent were followed three years or more, 52.3 per cent, five years or more, and 14.2 per cent, ten years or more.

In 1 of the 233 patients, carcinoma of the breast developed within one year. The history of this case follows:

CASE 45, GROUP A.—A married woman, aged 45, who had never been pregnant but whose menses had always been regular and normal, was admitted to the hospital because of a small, discrete, unattached mass in the right breast near the nipple. Four years before, a small fibro-adenoma had been removed from the same breast, close to the site of the new tumor. On local excision the new area proved to be simple cystic disease. Seven months later a small mass was discovered in the same breast in the upper and outer quadrant near the periphery. This was excised and found to be frank carcinoma. A radical amputation was performed one month later, and although histologic examination revealed the involvement of one axillary lymph node, the patient has remained free from recurrence for three and one-half years.

Among the 233 cases, there were 4 deaths, 3 of which were unrelated to carcinoma. Two of these patients (cases 28 and 179, belonging to the simple cystic group) died five and ten years after the operation, of suicide and apoplexy, respectively. The third (case 12, adenocystic group, grade I) was followed twelve years and died, according to her physician's report, of "heart and kidney trouble." The fourth patient (case 22, adenocystic group, grade I) died of carcinoma probably originating in the pelvis. Her history follows:

She was 37 years old and unmarried. There is no record of her symptoms or of their duration. At operation a mass of ½ × 1½ inches (1,767.8 cm.) was removed from the upper and outer quadrant of the right breast. The specimen (fig. 2 A) was sent to Dr. Bell, who made a diagnosis of cystic disease. The area illustrated is the only portion of the section which showed epithelial hyperplasia.

After two and one-half years, a small mass recurred in the same breast. Operation was repeatedly refused. Four and one-half years after excision the mass had increased slightly, and pain had developed in the pelvis and groins. Small inguinal masses appeared. A letter from the patient's physician stated that she died five years after the mammary tumor was excised, with large inguinal masses and with "generalized carcinomatous metastases" to the pelvis.

Series II: Fifty-seven patients were treated by simple amputation. Of 56 patients who were followed for periods ranging from two to twelve years, 96.4 per cent were followed three years or more, 64.2 per cent five years or more and 17.9 per cent ten years or more.

Two of these patients died, one of carcinoma of the breast and the other of "carcinoma of the stomach." The histories of these 2 cases follow:

CASE 23, GROUP A.—Two years previously a married woman, aged 42, had noted a small mass in the right breast. This had subsided spontaneously. Shortly before her admission to the hospital, a mass had again developed in the lower outer quadrant of the right breast. This was described as being of the size of a hen's egg and freely movable, with none of the clinical signs of malignancy. The breast was amputated and found to contain one large and numerous small cysts varying from microscopic dimensions to diameters of 5 mm. or more. The diagnosis of cystic disease was made by Dr. Bell. Approximately ten years later, generalized deep-seated pain developed. Examination revealed a heretofore undiscovered mass in the remaining breast. Roentgenograms of the skeleton demonstrated diffuse bony metastases. One year later the patient died of generalized carcinomatosis. Unfortunately, none of the slides or tissue blocks from this patient could be obtained for photographic reproduction.

CASE 5, GROUP B.—A married woman, aged 56, had one child, who had not been nursed. One month prior to her admission to the hospital she noticed bleeding from the right nipple. The examining surgeon found a small mass in the lower outer quadrant of the breast. The entire breast was removed, and the diagnosis of cystic disease was made. The patient moved out of the community and was

not seen again by the surgeon. A letter from her husband stated that she died one year later from what her attending physician diagnosed as carcinoma of the stomach.

Recurrences.—Recurrences in the same breast developed in 18 of the patients treated by local excision, new involvement in the opposite breast developed in 15 and both a recurrence and new involvement developed in 2 (table 10). Six of the 18 recurrent growths were treated by local excision and 4 by amputation. No treatment was given 8 patients. Seven of the 15 patients with new involvement underwent local excision; 2 were treated by simple amputation, and 1 by radical amputation under the mistaken clinical diagnosis of cancer. Five received no treatment. One of the 2 patients in whom recurrence and new involvement were combined was untreated; the other underwent simple amputation of the newly involved breast two years later and local excision of the recurrent mass three years later.

TABLE 10.—*Recurrences and New Involvements*

	Local Excision, Series I*						New Involvements, Simple Amputation Series	
	Recurrences			New Involvements				
	L. E.	S. A.	No Treatment	L. E.	S. A.	No Treatment	L. E.	S. A.
Group A........	5	3	6	5	1	4	1	4
Groups B and C	1	1	..	2	1	1	2	..

* One patient of group A had a radical amputation for a new involvement in the opposite breast. Two patients of group A had both recurrence and new involvement. One received no treatment. On the other local excision was performed for the recurrence and simple amputation of the newly involved breast.

In 7 of the patients treated by simple amputation masses subsequently developed in the remaining breast. Four were treated by simple amputation and 3 by local excision.

A slightly greater tendency to recurrence in the cases of adenocystic disease may be indicated by the finding of recurrences in 21.4 per cent of the combined adenocystic groups (groups B and C), as compared with recurrence in 13.9 per cent of the simple cystic group (group A). However, this difference is too small, and the discrepancy in the number of patients in the two groups too great, to warrant any definite conclusions.

Cystic Disease in Male Patients.—In addition to the cases already described, there were 9 cases of cystic disease in male patients, treated surgically. Their ages varied from 14 to 48 years. Since the epithelial element of the male breast is very limited and consists only of ducts near the nipple, the extent of the pathologic process is always confined to the area of the nipple or its vicinity. The largest lesion was described as being the size of a walnut. Previous masses had been removed in 2 instances. The patients were followed from three to fifteen years. All are living and well. There were no recurrences.

SUMMARY AND COMMENT

Two closely related problems merit discussion. The first is concerned with the diagnostic criteria for the differentiation of benign from malignant hyperplasia. The second is concerned with the probable course of the pathologic process when only the mass or a portion of it is removed and the breast preserved.

Diagnostic Criteria.—The difficulty which confronts a pathologist in the diagnosis of border-line tumors is well illustrated in the following 2 cases:

Mrs. M. R., aged 50, who had borne eleven children was admitted to the Minnesota General Hospital in July, 1926, complaining of a brownish discharge from the right nipple of seven months' duration. Both breasts were pendulous. The right was the larger and demonstrated diffuse nodularity with a definite indurated area above the nipple. Three small axillary lymph nodes were palpable on the same side. At exploration I removed a mass 5 cm. in diameter from the upper half of the breast. The diagnosis of adenocystic disease was made from a frozen section. The operative note describes the breast as the site of "diffuse cystic disease with the major area above the nipple. . . . the gross picture could be easily confused with carcinoma because of the hardness of the tumor." Local excision was performed. Four months later, because of a tumor mass medial to the scar, the patient consulted another surgeon at a private hospital. The recurrent mass was removed, and this time the diagnosis, made by another pathologist, was adenocarcinoma. A radical amputation was performed.

Recently I secured sections of the amputated breast and the axillary lymph nodes. No metastases were found in the nodes. Figure 2 B illustrates the section on which the diagnosis of carcinoma was made. Dr. Bell and Dr. O'Brien have reviewed this slide and reaffirm the original diagnosis of adenocystic disease. The patient was alive and well more than six years later.

Mrs. N. H., aged 39, presented herself for operation in February, 1929, for fibroid tumors of the uterus. Five years before a small area of cystic disease had been removed from the left breast, the diagnosis having been made in the department of pathology of the University of Wisconsin. A recurrence of the mass and a new involvement of the opposite breast had been under the observation of her surgeon for two years. Because of increasing induration he had decided to remove the recurrent mass. While the patient was convalescing from a hysterectomy, the mass was removed locally. From frozen sections, Dr. Bell made a diagnosis of adenocystic disease with probable early carcinoma. Simple amputation was performed, and 50 mg. of radium was inserted into the tissues about the wound. A later study of paraffin sections (figs. 2 C and D) did not eliminate a fear of the possibility that this breast harbored a malignant tumor. Consequently the simple amputation was converted into a radical amputation by the later removal of the axillary glands. The glands showed no evidence of metastases, and the patient is living and well at the time of writing. Dr. Bell has reviewed these sections and is convinced that the lesion is benign and represents only one of the extremely hyperplastic forms of adenocystic disease.

The first of these cases illustrates a difference of opinion between pathologists, while the latter illustrates the natural unwillingness to subject a patient to the risk of an inadequately treated malignant condi-

tion, even though it seems highly probable that the lesion is benign. They are excellent examples of border-line lesions.

Bloodgood (1931) has pointed out that when the diagnosis of malignant growth can be easily made, the course of the disease and its prognosis are characteristic of cancer. When the tumor is of doubtful nature, and the diagnosis is subject to disagreement, the glands are, with the rarest exception, not involved, and the patient survives regardless of the type of treatment.

Slight damage is done to the true picture of either cystic disease or carcinoma if these border-line cases, even though radical amputation is performed, are set apart as a separate group. Their inclusion and acceptance as cases of true malignant changes increase the percentage of cases in which carcinoma is described as arising in an area of cystic disease. Bell estimates the incidence of such occurrence at 3 per cent of all cases of malignant changes, an incidence only slightly higher than the incidence of carcinoma in the normal breast as shown by vital statistics for the year 1929.

Also, by assuming that the lesions represent cancers of low malignancy, one is given a false impression of the curability of cancer. The necessary and commendable conservatism on the part of pathologists restricts the rapid acquisition of knowledge concerning these questionable tumors. Future progress, and the only method by which the field of benign lesions can be enlarged at the expense of the border-line group, lies in the frequent interchange of slides between pathologists and in the publication of photomicrographs of lesions the clinical course of which has already been determined.

Gradually, as confidence grows and as circumstances—such as the refusal of patients to accept, or the inability to withstand, radical operation—add cases of border-line tumors ·in which limited operations are done, the diagnostic criteria may be shifted in a direction which will increase the benign group and diminish the malignant group.

The diagnostic criteria which have been generally adopted and utilized in the hospitals from which the material here presented was obtained are those of the department of pathology at the University of Minnesota, which teaches that the diagnosis of cystic disease depends largely on the preservation of the lobular arrangement of the breast. Almost any degree of hyperplasia may occur so long as it is confined to lobules. A certain reservation is made in the type of cystic disease producing papillomatous growths in the larger ducts. The difficulty in differentiating this lesion from cancer of the duct has resulted in the recommendation of the complete operation in a number of cases in which it was felt that the lesion was probably benign. Bloodgood (1921) has demonstrated limited invasion of connective tissue in lesions the benign nature

of which he has established by clinical follow-up. Thus far we have been unwilling to overlook invasion as a sign of malignant change.

Figures 3 A, 3 C, 4 A and 4 C illustrate lesions which a large proportion of surgical pathologists would call benign, but which some would undoubtedly label as malignant. Attention is called to the greater diagnostic value of low magnifications. Figures 3 B, 3 D, 4 B, 4 D and 6 B represent photomicrographs of lesions shown with lower magnification in figures 3 A, 3 C, 4 A, 4 C and 6 A. With a high magnification the differentiation from cancer is difficult or impossible without the knowledge, revealed by low power magnification, that the epithelium is everywhere confined to the ducts or acini.

The picture of cystic disease should not be confused by the presence of hyperplastic forms of the sweat gland type. These structures are frequently encountered in association with all forms of the disease. Figure 1 C illustrates a group of acini of the sweat gland type occurring in simple cystic disease. Figure 1 D illustrates the same process associated with adenocystic disease. The degree of epithelial activity in these glands is approximately the same, regardless of the activity of the normal-staining epithelium. They are not regarded as precancerous.

Since it is considered that local excision or simple amputation is insufficient to cure true carcinoma, 290 followed cases in which the accuracy of the diagnosis is verified are presented. In none did local cutaneous, axillary or supraclavicular metastases develop, as would be anticipated in the event that a malignant condition had been mistaken for cystic disease.

In 1 patient (case 75, series I, group A) carcinoma developed seven months after the removal of an area of cystic disease. That these represented separate lesions is indicated by the fact that the area of cystic disease was small, of the simple type and located near the nipple, while the malignant growth was of the undifferentiated infiltrating variety, occurring at the edge of the breast near the axilla.

One patient (case 23, series II, group A) who died of generalized metastases eleven years after simple amputation of one breast can logically be considered as having had in the other breast a carcinoma which had gone unrecognized, although the possibility must be entertained that the proper block of tissue from the amputated breast was not received for diagnosis.

In the absence of local cutaneous metastases and of axillary or supraclavicular metastases the death in case 22, series I, group B, cannot be accepted as due to carcinoma of the breast. The presence of inguinal masses and the physician's description of carcinoma in the pelvis suggest that death was due to carcinoma originating in the pelvis.

TABLE 11.—*Series I, Patients Treated by Local Excision (Group A, Simple Cystic Disease)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	25	M	....	L	....	....	....	....	....	7	....	
2	39	M	2 weeks	L	No	....	Yes	....	....	6	Same breast, 5 years later	
3	41	S	6 weeks	M	Yes	....	No	No	....	9	....	
4	44	M	3 months	....	Yes	....	No	No	....	9	....	
5	55	M	10 days	L	No	....	....	No	....	4	....	
6	45	S	1 week	L	No	....	Yes	No	....	2	....	
7	42	M	3 months	B-M	Yes	....	Yes	....	....	7	....	
8	29	M	....	....	....	....	....	....	....	3	Same breast, 2 years later	
9	56	M	5 years	L	Yes	B†	Yes	No	....	3	....	Only one breast operated on; some pain since operation
10	..	M	1 year	....	....	:S	....	....	....	9	....	Some pain since operation
11	50	S	....	L	Yes	.	No	No	....	6	....	
12	32	S	4 days	L	No	.	No	No	Opposite breast, local excision 2 years previously	8	....	
13	41	S	4 weeks	L	No	....	No	No	....	12	....	
14	25	S	3 weeks	D	No	....	No	No	....	12	....	
15	49	M	....	L	....	....	Yes	No	....	7	....	
16	25	M	6 months	L	....	....	Yes	....	....	5	....	
17	39	M	3 weeks	M	Yes	....	Yes	....	....	5	....	
18	38	M	2½ years	L	No	....	Yes	2	....	4	....	Had two pregnancies after first operation
19	21	M	4 months	M	No	.	Yes	....	Opposite breast, local excision 6 years previously	3	....	
20	44	S	3 months	B-L	No	.	No	....	Same breast, abscess at lactation 4 months previously	5	....	Bilateral local excision
21	42	M	....	L	....	.	No	No	Opposite breast, radical amputation 2 years previously for carcinoma	2½	....	
22	47	M	1 week	L	No	....	Yes	No	....	3	....	
23	40	S	2 weeks	L	....	....	No	No	....	5½	....	
24	37	S	9 months	:L	....	....	No	No	Opposite breast, local excision 1 year previously	7	....	
25	50	M	2 weeks	L	No	....	Yes	....	....	5	....	
26	43	M	....	M	....	....	Yes	....	....	6	....	Tuberculous glands of same axilla several years previously
27	46	M	2 weeks	L	No	....	No	No	....	12	....	
28	40	M	....	L	No	....	Yes	....	....	10	....	
29	28	M	3 days	M	....	....	No	Yes	Opposite breast, local excision 4 years previously	3	....	
30	36	M	1 week	L	No	....	No	No	....	3	....	
31	33	M	4 months	L	No	....	Yes	....	....	3	....	Died 10 years later; "paralytic stroke"
32	47	M	....	L	Yes	....	....	No	....	3	....	
33	32	M	6 months	L	Yes	..	No	No	Opposite breast, local excision 4 years previously	8	....	
34	42	S	1 month	L	No	..	Yes	....	....	8	....	
35	37	S	4 months	L	No	..	No	No	Opposite breast, local excision 4 years previously	6	....	
36	33	M	....	....	....	..	Yes	....	....	5	....	
37	39	S	....	:L	....	..	No	No	....	4	....	
38	:0	M	....	....	....	..	....	:No	....	4	....	

No.	Age	Sex	Duration	L/D				Previous history	No.	Later history	Remarks
39	45	M	6 weeks	D	No	No	No	Opposite breast, local excision 3 years previously	4	....	
40	..	M	3 months		No	..	..	Same breast, abscess at lactation 10 years previously	10	....	
41	40	M	4 days	L	Yes	Yes	..	....	2	Opposite breast, local excision 1 year later	
42	23	S	1 year	L	No	No	..	....	6	....	
43	47	M	2½ years	L	Yes	Yes	No	....	9	....	
44	33	S	4 days	L	Yes	Yes	No	....	3	....	
45	31	M	1 week	..	No	No	No	....	6	....	
46	42	M	....	..	..	..	..	....	9	....	
47	46	M	....	..	No	Yes	No	Same breast, local excision 6 years previously	9	....	
48	49	M	....	L	Yes	No	No	....	2	....	
49	48	M	10 days	L	No	No	No	....	12	....	
50	37	L	....	L	No	No	No	....	9	....	
51	50	S	1 day	L	Yes	Yes	..	....	14	....	
52	45	M	....	L	Yes	No	..	Opposite breast, local excision 1 year previously	3	....	
53	49	M	....	..	..	Yes	No	....	10	Opposite breast, mass 6 years later	Some pain since operation
54	60	S	1 day	L	No	No	No	....	8		
55	41	M	8 months	L	No	Yes	No	....	3	Same breast, simple amputation 3 years later	
56	22	M	2 months	..	Yes	Yes	No	....	10	Opposite breast, local excision 4 years later	
57	35	S	1 month	..	No	No	No	....	9	....	
58	37	M	....	L	No	..	No	....	7	....	
59	40	M	2 months	L	Yes	Yes	No	....	6	Opposite breast, simple amputation 2 years later; same breast, local excision 3 years later	
60	31	S	....	L	No	No	No	....	11	....	
61	30	M	....	L	No	No	No	....	4	....	
62	41	S	....	M	Yes	Yes	No	....	2	....	
63	25	S	1 week	L	No	No	No	....	2	Opposite breast, mass 3 years later	
64	63	M	2 months	L	Yes	Yes	..	....	3	....	
65	28	S	2 months	L	Yes	Yes	No	....	11	....	
66	20	S	....	L	No	No	No	....	13	Same breast, recurrence; opposite breast, new mass 7 years later	
67	40	S	1 week	L	No	No	No	....	4	....	
68	55	M	15 years	L	Yes	Yes	Yes	....	8	....	
69	45	S	1 month	L	No	No	No	....			
70	40	S	5 months	M	..	Yes	..	....	8	Opposite breast, simple amputation 7 year later	
71	22	M	1 year	..	Yes	Yes	No	....	9	....	
72	40	M	3½ months	..	No	..	..	....	6	Same breast, local excision 7 months later; diagnosis, carcinoma; radical amputation the next month	
73	31	M	4 months	L	No	Yes	No	Same breast, local excision 4 years previously	13	....	
74	38	M	20 years	..	No	No	..	....	..	....	
75	45	M	....	L	Yes			....			
76	50	M	2 weeks	L	No	No	No	....	2	....	
77	31	M	....	L	No	No	..	....	3	....	

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
78	36	S	2 years	L	No		No	No	Opposite breast, local excision 8 years previously	4		
79	27	M	2 years	L	Yes		Yes	No		6	Same breast over 1 year later, 3 subsequent local excisions, final one removing remainder of breast tissue	
80	46	M	5 days	L	No		Yes	No		4½		
81	20	S	2 months	L	No		No			3		
82	33	M	7 years	L	No					5	Bilateral simple amputation 2 years later	
83	62	M	1 year	B-L	No		Yes	No		2		
84	42	M	1 year	L	Yes				Opposite breast, radical amputation 1 year previously for carcinoma with axillary metastases	7		Bilateral local excision
85	39	M	2 months	B-L	No		Yes			14		
86	40	M	3 months	B-L				No		6		Bilateral local excision
87	36	S	2 months	B-L	No		No	No		5		Bilateral local excision
88	40	M		L	No		Yes	No		11		Only one breast operated on
89	25	M	1 year	L	No		No	No		2	One breast, recurrence	
90	42	M	1 week	L	No		No	No		2		
91	37	S	3 weeks	L	No		Yes	No		2		
92	41	M	5 months	L	No		No			2	Same breast, recurrence	
93	30	M	1 week	L	No		Yes			3		
94	30	S	6 days	L	Yes					4		
95	42	M		B-L	No			No		4	Opposite breast, local excision 3 years later	
97	62	M	3 months		Yes			No	One breast, local excision 14 years previously	2		Bilateral local excision
98		S								10		
99	48	S		B-L	Yes		No			5		Some pain since operation
100	42	M	2 months	L	No		No	No		5		Only one breast operated on
101	32	M	3 months	L	No		No			14		
102	32	S		L	No					3	Same breast, recurrence	
103		M	3 months	L						3	Opposite breast, mass 2 years later	
104	47	M		L	No		No	No		3		
105	38	M	5 days	L	No		Yes			0		
106	38	S	4 months	L	Yes		No	Yes		11		
107	23	S	2 months	L	No		No	No		3		
108	43	M	2 weeks	L	No			No		5		
109	25	M	2 weeks	L	No		Yes	Yes		13		
110	43	S	3 days	L	No		No	No		3		
111	31	M		L	No		No	No		11		
112	40	M	3 months	L	No		No	No	Opposite breast, local excision 2 years previously	2	Opposite breast, local excision 11 years later	
113	30	M	8 months	L	Yes					2		

No.	Age	Cond.	Duration	Side				No.	Notes	Remarks
111	21	M	3 months	L	Yes		Yes	3		Opposite breast, mass 3 years later
115	31	M	3 months	L	No		Yes	2		In the three subsequent pregnancies breast did not lactate
110	40	M	7 years	L	No		Yes	6		
117	30	M	1 week	L	No		No	4		Some pain since operation
118	42	M	....					7		
119	30	M	2 months					7	Same breast, local excision 2 months later	
120	40	S	6 days	L	No		No	10		Opposite breast, local excision 2 years later
121	32	M	....	L	No		Yes	5		
122	26	M	2 weeks	L	No		Yes	12		
123	21	S	....				No	3		
124	40	M	....	L				3		
125	33	M	3 days	L	No		Yes	4		
126	61	M	2 years	L	Yes		Yes	6		
127	31	M	15 years	L	Yes		No	5		
128	61	M	5 years	L	Yes		Yes	12		
129	38	M	....	L	Yes	s	Yes	8	Same breast, abscess at lactation 5 years previously	
130	30	M	....	L	Yes		No	4		
131	42	M	3 months	L	Yes		No	6		
132	29	M	3 months	L	No		No	6		Menopause at 19 years; injury to spine
133	45	M	3 months	L	Yes		No	3		
134	53	S	10 days	L						
135	37	M	....		Yes		No	2		
136	43	M	1 day	L	No		No	6		
137	48	M	6 months	L	Yes		Yes	8		
138	62	M	2 days	L	Yes		Yes	9		
139	45	M	1 week	B-L	Yes		No	7		
140	35	M	....			B		7		
141	43	M	3 years	L	No		No	3	Same breast, infection 2 years previously at lactation	
142	62	M	4 months	L	Yes		Yes	14		
143	29	M	2 years	L				7		
144	35	M	4 months		No		No	6		Only one breast operated on; enlarged gland in axilla
145	46	M	2 years	L	Yes		Yes	5		
146	51	M	10 months	L	Yes		Yes	10		
147	47	M	1 month	L		1		12		Some pain since operation
148	22	S	....			1		4	Same breast, local excision 2 years later; same breast, recurrence	
149	21	S	3 years		No		No	7		
150	33	M	1 day	L	Yes		Yes	8		Married since; nursed child. Some pain since operation
151	31	S	6 weeks	L				7		
152	44	S	....		No		No	9		
153	40	M	6 weeks	L	No		Yes	11		Tuberculous glands of axilla removed at same time
154	55	S	2 months	L	No		Yes	5		
155	33	S	1 week	L	Yes		No	5		
156	43	M	2 weeks	L	Yes		Yes	4		
157	52	M	2 weeks		No		No	3		
158		S	....					5	Same breast, local excision 2 years previously	

TABLE 11.—Series I, Patients Treated by Local Excision (Group A, Simple Cystic Disease)—Continued

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
159	34	S	6 weeks	L	No		No	No		7		
160	48	M	2 days	L	No		No	No	Opposite breast, local excision 2 years previously	9		
161	42	M	1 week	L	No		Yes	No		3	Opposite breast, local excision 1 year later	
162	37	M	2 days	L	No	Yes	Yes			4		
163	40	M	2 weeks	L	No	Yes	Yes			5		
164	44	M	3 weeks		No	No	Yes	No		3		
165	35	M	1 month			Yes	Yes	No		4		
166	44	S		L		No	No	No	Opposite breast, local excision 1 year previously			Some pain since operation
167	30	S	7 months	M	Yes	No	No	No	Same breast, local excision 4 years previously	5	Same breast, local excision 3 years later	
168	22	S	3 years		No	Yes	Yes					Only one breast operated on
169	40	M	8 months	L		Yes	Yes	No				
170	46	M	2 months	B-M		No	No	Yes				
171	47	S	6 years	M		Yes	Yes				Bilateral local excision five years later committed suicide; insane	
172	24	M	1 month	L		No	No	Yes	Opposite breast, simple amputation 7 years previously			
173	44	M		L		No	No					
174	30	M	6 weeks	L		No	No	No				
175	48	M	3 weeks	L		Yes	Yes	No				
176		S	3 years	L		No	No	No				
177	29	M		M	No	Yes	Yes	No				
178				B-L	No	No	No	Yes				Only one breast operated on
179	46	M										
180	41	S	3 months	L	Yes	Yes	Yes	No	Same breast, local excision 16 months previously; opposite breast, simple amputation 3 years previously			
181	37	M	3 years	L	No	No	No	No			Same breast, recurrence 1½ years later	
182	48	M	6 weeks	L	Yes	Yes	Yes	Yes				
183	42	M	4 months	L	Yes	Yes	Yes	No				
184	28	M	5 days	B-M	Yes	Yes	Yes	No				Some pain since operation, simple local excision, right breast.
185	37	S		L		No	No	No				Left breast, local excision, right breast, cystic disease
186	39	S	1 month	L		Yes	Yes	Yes				simple amputation, cystic disease
187	51	M		L								disease and adenoma
188	43	S	6 weeks		Yes		No	No				
189	33	M	1 year		No		Yes	Yes				
190	34	M	6 months	L-L	Yes		Yes	No				
191	54	M		B			No	No	No 2			

* L denotes local, M multiple, B bilateral and D diffuse involvement.
† Bloody.

After a consideration of the literature, it seems obvious that the criteria here used represent entirely different standards for the diagnosis of malignant tumors from those used by many writers.

That pathologists are revising their diagnostic criteria is shown by Bloodgood who in 1915 and again in 1930 submitted sections of borderline tumors to able and prominent pathologists. Whereas in 1915 the majority of sections had been considered malignant, in 1930 most pathologists considered them benign.

It may reasonably be concluded that in this series of 290 cases, the diagnosis of benign lesions has been substantiated by the clinical course of the disease and that the diagnostic criteria as established at the University of Minnesota have thus far proved safe.

Probable Course of the Disease.—In drawing conclusions relative to the risk of malignant change occurring in cystic disease, we are justified in using cases in which only the clinically recognizable or grossly pathologic areas have been removed. The tendency of the process to extend and to involve the opposite breast is generally recognized (Reclus [1883], Schimmelbusch, Lichtenhahn, Cheatle [1930], and others). The high incidence of recurrence is consistent with this tendency. Furthermore, the pathologic process is always more extensive than the clinical or gross pathologic observations indicate (Brissaud [1888], Saar, and others). Tietze (1904) and Goens-Rosales found a high incidence of cystic changes in elderly women without clinical evidence of the disease, while Askanazy (1925) found a similar high incidence, not only in senile breasts, but in the breasts of women under 40. It is probable that local excision of clinically recognizable lesions never effects a cure in patients with cystic disease.

The recognized tendency toward bilateral involvement renders the 57 cases in which simple amputation was performed of some value, but the greatest dependence in determining the risk of subsequent malignant change must be placed on series in which the breasts have been preserved. Of 233 cases of this type carcinoma of the breast developed in only 1. For reasons previously outlined, this development is reasonably considered coincidental with rather than an outgrowth of the previous disease process.

Of the 233 patients, 43, or 18 per cent, had lesions composed of forms in which epithelial hyperplasia was active or in which it dominated the picture. In none of these breasts did carcinoma subsequently develop. There is no evidence to support the view held by Semb, Kilgore (1928) and others that this form, in contrast to simple cystic disease, is susceptible to malignant change.

Aside from showing the suggested greater tendency of hyperplastic forms to recur and to involve the opposite breast, nothing was learned and no advantage was gained by separating and grading adenocystic

TABLE 12.—*Series I, Patients Treated by Local Excisions (Group B, Adenocystic Disease, Grade I)*

Patient	Age	Marital State	Duration of Symptoms	Distribution	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	22	M	1 year	L*	Yes			No		5		
2	30	M	16 years	L	No		Yes			7	Opposite breast, local excision 18 months later	
3	40	M	2 days	L	Yes		Yes	No		2½	Opposite breast, radical amputation 2 years later; no carcinoma	
4	47	S	3 weeks	L	No		No	No		11		
5	46	M	3 weeks	L	No	No		No		3		
6	33	S	3 months	L	No	No	No	No		6		
7	45	M	1 week	L	Yes	Yes				9		
8	34	M	3 months	L	Yes	No	Yes			7		
9	33	M	2 weeks	L	No	No	B†	3		12		Axillary mammary gland enlarged with each pregnancy
10	24	M		L								Some pain since operation
11	43	S	1½ years	L	No	No	No	No		12		Died 12 years later; "heart and kidney trouble"
12	22	S	3 months			No		No		3	Opposite breast, simple amputation 2 years later	
13	29	M		L	Yes	Yes	Yes	Yes		3		
14	39	M	10 years	L	No	No			Opposite breast, local excision 4 months previously	2	Opposite breast, local excision 4 years later	
15	30	M	1 week	L	Yes	No	Yes	No		4		
16	50	M	4 months			No	B			3		
17	50	M			Yes		7			8		
18	43	M		L	Yes	Yes		Yes		5		
19	39	M	3 weeks	L	Yes	Yes	Yes	No		3	Same breast, recurrence 2 years later	
20	33	M	3 months	L	No	Yes	No			3		Some pain since operation
21	38	S	1 year	L						5	Opposite breast, mass 4 years later	
22	37	M								3		Some pain since operation
23	41	M			L	No	No	No		3		Some pain since operation
24	40							No	No	5		
25	25	S				No	No	Yes	No	3		Died 5 years later; pelvic metastases
26	56	M	3 weeks			No	Yes	Yes	No	8	Same breast, local excision 5 and 10 years later	
27	50	M				No		Yes	No	0		
28	65	M	1 day							10		
29	47	M			L							

* Local involvement.
† Bloody.

TABLE 13.—Series I, Patients Treated by Local Excision (Group C, Adenocystic Disease, Grade II)

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Preg-nancies	After Preg-nancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	22	S	....	L	No	:	No	:	....	3	....	
2	31	M	5 days	L	No	:	No	No	....	10	....	
3	23	S	2 years	B-L	No	:	No	Yes	....	12	Same breast, recurrence	Only one breast operated on Some pain since operation
4	29	S	2 years	:	Yes	:	No	:	....	3	....	
5	65	M	6 months	L	No	:	No	No	....	5	....	
6	33	S	10 years	M	Yes	:	No	No	....	4	....	
7	42	M	....	L	:	:	:	:	....	3	....	
8	43	M	2 years	B-L	No	:	:	:	....	3	Same breast, simple amputation 2 years later	Bilateral local excision
9	35	S	1 week	L	Yes	:	:	:	....	2	....	
10	21	S	3 months	:	:	:	No	2	....	3	....	
11	30	S	3 years	L	No	:	No	No	....	5	....	
12	21	S	1 month	L	No	:	No	:	....	2	....	
13	27	M	2½ years	:	No	:	:	:	....	2	....	

* L indicates local, B bilateral and M multiple involvement.

TABLE 14.—*Series II, Patients Treated by Simple Amputation (Group A, Simple Cystic Disease)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Pregnancies	After Pregnancies	Previous Lesions	Follow-Up, Years	Subsequent Involvement	Comment
1	45	S	3 days	D	No	:	No	No	....	12	....	
2	46	M	Several months	L	...	:	...	:	....	5	....	
3	25	M	1 month	L	Yes	:	Yes	:	....	5	Opposite breast, local excision 2 years later	
4	37	S	3 weeks	..	Yes	.	No	No	....	3	....	
5	41	M	....	B-M	...	:	Yes	...	Both breasts, local excision 5 years previously	8	....	Bilateral simple amputation
6	38	S	....	L	...	:	No	No	....	0	....	
7	30	M	2 weeks	L	No	:	No	No	....	0	....	
8	34	M	6 months	D	No	:	...	:	....	7	....	
9	36	M	2 weeks	M	No	:	Yes	No	Same breast, mastitis 16 years previously	3	....	
10	31	M	6 years	L	No	:	Yes	:	Same breast, local excision 9 years previously	4	....	
11	30	S	9 years	..	Yes	B†	No	No	....	4	....	
12	46	M	4 days	L	No	:	...	:	....	3	....	
13	40	M	2 months	L	...	:	10	1	Same breast, abscess previously	8	....	
14	29	M	1 year	L	No	:	Yes	No	....	0	....	
15	44	M	....	M	No	:	Yes	No	....	8	....	
16	38	M	2 months	..	No	:	Yes	No	Opposite breast, radical amputation 6 months previously; adenocarcinoma	0	Opposite breast, simple amputation 4 months later	
17	43	M	6 months	L	Yes	:	Yes	:	....	3	....	
18	44	M	2 years	D	No	:	...	:	Opposite breast, radical amputation 2 years previously	6	....	
19	:	M	2 months	:	...	:	Yes	Yes	....	0	....	
20	45	S	5 days	M	No	:	No	No	....	3	....	

No.	Age		Duration	Inv.					Previous operation		Remarks
21	38	M	....	:	:	:	...	...	Same breast, local excision twice 2 years previously	10	....
22	47	S	1 week	No	No	:	No	No	....	11	Died 11 years later; metastases to bone
23	42	M	2 years	No	No	:	No	...	....	11	....
24	33	M	5 months	D	Yes	:	Yes	...	Same breast, local excision 2 years previously	3	....
25	39	M	....	L	No	:	No	:	Same breast, local excision 6 years previously; opposite breast, simple amputation	3	....
26	48	S	3 weeks	L	No	:	No	No	Opposite breast, simple amputation 2 years previously	10	....
27	46	S	3 months	M	Yes	:	No	No	....	11	....
28	40	S	3 months	L	...	:	Yes	No	....	5	....
29	:	M	2 weeks	L	Yes	:	Yes	:	....	0	....
30	31	M	12 years	D	Yes	:	Yes	:	....	2	....
31	45	M	4 days	L	Yes	:	Yes	No	Opposite breast, simple amputation several years previously	7	....
32	40	M	3 years	:	...	:	...	:	Opposite breast, simple amputation 4 months previously	6	....
33	52	M	6 weeks	M	No	:	Yes	No	Opposite breast, simple amputation 4 months previously	8	....
34	39	S	....	M	...	:	No	No	Opposite breast, simple amputation 1 year previously	4	Opposite breast, simple amputation 2 months later
35	37	S	....	:	No	:	No	No	....	12	....
36	46	M	3 months	L	No	:	...	:	....	5	....
37	54	M	3 months	:	Yes	:	...	No	Same breast, local excision 4 months previously	9	Opposite breast, simple amputation 2 years later
38	41	M	1 year	:	...	:	...	:	Opposite breast, simple amputation 1 year previously	3	....
39	45	M	....	L	...	:	...	:	....	7	Opposite breast, simple amputation 6 months later
40	34	S	10 days	L	No	:	No	No	....	4	Opposite breast, simple amputation 6 months later
41	37	M	1 year	L	No	:	No	No	....	6	....
42	40	M	6 months	M	No	:	Yes	No	....	5	Before operation 4 series of high voltage roentgen treatments had been given with no benefit

* D denotes diffuse, L local, B bilateral, and M multiple involvement.
† Bloody.

TABLE 15.—*Series II, Patients Treated by Simple Amputation (Group B, Adenocystic Disease, Grade I)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Preg- nancies	After Preg- nancies	Previous Lesions	Follow- Up, Years	Subsequent Involvement	Comment
1	39	M	6 months	M	No	:	:	No	....	3	....	
2	40	M	3 weeks	D	Yes	:	:	:	....	3	....	
3	31	M	6 months	L	Yes	:	Yes	Yes	Same breast, abscess 10 years previously	11	....	
4	50	M	6 months	D	No	B†	No	No	....	10	Died 1 year later; carcinoma of stomach	
5	56	M	1 month	:	No	:	Yes	No	....	..	....	
6	47	S	4 days	L	No	:	No	No	Same breast, local excision 6 weeks previously	4	....	
7	56	S	....	D	No	:	No	No	....	4	....	
8	38	M	2 years	M	No	:	No	No	....	2	....	

* M denotes multiple, D diffuse and L local involvement.
† Bloody.

TABLE 16.—*Series II, Patients Treated by Simple Amputation (Group C, Adenocystic Disease, Grade II)*

Patient	Age	Marital State	Duration of Symptoms	Distribution*	Pain	Discharge	Before Preg- nancies	After Preg- nancies	Previous Lesions	Follow- Up, Years	Subsequent Involvement	Comment
1	45	M	1 year	D	Yes	B†	Yes	No	....	4	Opposite breast, local excision 3½ years later	
2	57	M	3 years	L	No	B	Yes	No	....	4	....	
3	32	M	3 months	L	No	:	Yes	No	....	5	Opposite breast, local excision	
4	48	M	3 months	L	No	:B	Yes	No	....	7	Opposite breast, local excision 6 years later	
5	29	S	....	:	No	....	No	No	....		....	
6	30	S	2 years	M	Yes	:	No	No	Opposite breast, simple ampu- tation 2 years previously	11	....	
7	40	M	9 months	M	No	:	....	No	....	5	....	Some pain since operation

* D denotes diffuse, L local and M multiple involvement.
† Bloody.

disease. Of the 57 patients treated by amputation, carcinoma probably developed in the opposite breast of 1 patient, making a total incidence of 2 cases of carcinoma of the breast in 290 of the patients who were followed, or 0.7 per cent.

CONCLUSIONS AND RECOMMENDATIONS

The evidence here advanced justifies the following conclusions:

Cystic disease is not a precancerous lesion, and malignant changes are no more likely to develop in a breast showing the disease than in one which is entirely normal. No evidence was obtained from this material to justify the contention that the adenocystic form of the disease is more dangerous than the simple cystic form.

Diagnostic criteria which have withstood the clinical test of time are available and justify a more liberal interpretation of the histologic picture in favor of benignancy.

The adaptation of these views to the treatment of cystic disease will still allow considerable latitude in the procedures recommended.

One may approach the problem of treatment with the easy philosophy that the total removal of mammary tissue will for all time relieve the patient of worry and risk, and the surgeon of responsibility. However, it is assumed as basic that the preservation of the breasts, both from the functional and the cosmetic standpoint, is desirable and commendable if it can be accomplished with reasonable safety to the patient.

From the standpoint of risk of malignant degeneration, there is no more justification for the amputation of breasts containing cystic disease than for the routine removal of normal breasts to prevent the inevitable occurrence of carcinoma in approximately 2 per cent of cases.

Using the word "conservative" in its broadest meaning and endowing it with all surgical virtue, I have formulated the following policy as representing the conservative attitude toward cystic disease of the breast. It is based on the fear that carcinoma may be present and unsuspected at the time of examination, rather than on the fear that a malignant condition will subsequently develop. It calls for an exploratory incision and limited operations frequently and only rarely for amputations. It throws a great burden on the pathologist and demands his thorough familiarity with the various forms of cystic disease which may simulate malignancy. It is designed to afford the patient the maximum protection with the minimum anatomic and functional loss.

All single solid tumors in a woman over 25 years of age should be removed for diagnosis. While, as Ewing has stated, the diagnosis of carcinoma can, in the majority of cases, be made from the gross tissue at the operating table, a competent pathologist with facilities for examining frozen sections should be available for the 10 or 20 per cent of cases in which this is not possible.

Single small localized areas, even though clinically characteristic of cystic disease, are better examined by a biopsy. Under the age of 25 malignant tumors are so rare that in the absence of clinical signs of malignancy there is no need for operation, or at least operation may be delayed.

While the presence of multiple tumors in one or both breasts is strong evidence of the benign nature of a process, I prefer to remove one or more of the most suspicious on the basis that if carcinoma is developing in a breast containing benign masses, it can only be recognized clinically after it has become characteristic and hence after late signs of malignancy have developed. By excising the most suspicious area the danger is not obviated, but it is minimized.

Cysts sufficiently large to be recognized clinically or by transillumination also strongly indicate benignancy. The incidence of 5 carcinomas in 500 cases of blue-domed cysts was reported by Bloodgood (1929). In each case it was the malignant tumor which was palpated and operated on. The cysts were only accidentally discovered at operation.

There is a sufficiently large number of reported cases, however, in which cancer developed in the wall or in the immediate neighborhood of a cyst (Bartlett [1924], Adams, McGlannan, Fitzwilliams and others) to make the excision of a single cyst advisable. When cysts are multiple, the risk involved does not warrant an extensive procedure or the loss of the breast.

There is an increasingly large number of patients with a condition so characteristic that no operation is recommended. The best example of this is the diffuse form of cystic disease, the shotty or nodular breast, the greater part of one or both breasts being involved and no one area standing out more definitely than another. Such patients need not be operated on, but must be closely observed.

When one area in a diffuse process stands out more prominently or when, under observation, an area develops and becomes more prominent, exploratory incision and biopsy are indicated. The remainder of the breast is of no value in determining the nature of this newly developing portion.

Bleeding from the nipple demands the localization of the source of the blood and the removal of that portion of the breast for diagnosis. Over 50 per cent of such cases will prove benign. When the sources are multiple, it may be necessary to remove the breast. This course is dictated not through fear that malignant changes will develop, but rather because they are already established and responsible for a part of the bleeding. The radical operation should be performed only when malignancy is proved.

In applying these principles the age of the patient must be given some consideration. What is a conservative procedure in a woman of 30 is not necessarily so in one of 50. In the older woman the period

of function is past, the loss of the breast is not of such vital concern, and the risk of developing cancer is greater.

For this reason I believe that in certain instances simple amputation of the breast is justified. Particularly is this true when limited excision does not remove the entire process, and when the consistency of the remaining mammary tissue so obscures a developing carcinoma that the patient would lose her greatest opportunity for an early diagnosis and cure.

There can be no compromise with the dictum which demands radical operation in all cases in which histologic examination still leaves the experienced pathologist in doubt.

Greater knowledge and altered diagnostic criteria will in the future cause fewer unnecessary radical amputations to be performed.

In view of the limitations imposed on clinical methods of diagnosis, the procedures outlined seem reasonable and are consistent with my conception of what is best for the patient.

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PEPTIC ULCERS

COMPARATIVE FREQUENCY AFTER DEPRIVATION OF BILE AND
PANCREATIC JUICE

BENJAMIN N. BERG, M.D.

NEW YORK

During the past few years, in connection with other investigations,
I examined a number of animals deprived of their pancreatic secretions
by means of fistulas, ligation of the pancreatic ducts and pancreatectomy
and was impressed by the infrequent occurrence of peptic ulcers in
these animals compared with dogs in which bile was excluded. In 1926,
Kapsinow [1] produced duodenal ulcers in seventeen of forty-three dogs
by excluding bile from the intestine by means of cholecystonephrostomy,
with ligation and division of the common duct. In 1930, Berg and
Jobling [2] observed that peptic ulcers developed in ten of twenty-three
dogs with biliary fistulas and biliary obstruction. Bollman and Mann [3]
reported the occurrence of peptic ulcers in sixty-four of eighty-seven
dogs with jaundice after ligation of the common duct. Kim and Ivy [4]
found ulcers in six of ten dogs with biliary fistulas. Loewy [5a] observed
duodenal ulcers in three of ten dogs deprived of bile by means of fistulas
and by choledocho-ureteral anastomosis. Hosomi [6] and Ivy, Schrager
and Morgan [7] found duodenal ulcers in dogs after plastic operations

1. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclu-
sion of Bile from the Intestine, Ann. Surg. **83**:614 (May) 1926.

2. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic
Ulcers; Experimental Study, Arch. Surg. **20**:997 (June) 1930.

3. Bollman, I. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstruc-
tive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

4. Kim, M. S., and Ivy, A. C.: Prevention of Experimental Duodenal Ulcer
by Feeding Neutral Gastric Mucin, J. A. M. A. **97**:1511 (Nov. 21) 1931.

5. Loewy, G.: (a) Production expérimentale d'ulcères duodénaux par déri-
vation isolée de la bile, Bull. et mém. Soc. nat. de chir. **57**:739 (May 20) 1931;
(b) Influence de la dérivation du suc pancréatique sur la production des ulcères
duodénaux, Compt. rend. Soc. de biol. **111**:783 (Dec. 3) 1932.

6. Hosomi, K.: Ueber das sogenannte peptische Geschwür des Magens und
Duodenums beim Hunde, das gelegentlich der Choledochusplastik entsteht, Vir-
chows Arch. f. path. Anat. **267**:726 (March 21) 1928.

7. Ivy, A. C.; Schrager, V. L., and Morgan, J. E.: Spontaneous Duodenal
Ulcers in Dogs with Chronic Mild Icterus and Hepatitis, Proc. Soc. Exper. Biol.
& Med. **30**:698 (March) 1933.

on the common duct, which were usually accompanied by evidences of biliary obstruction.

Relatively few reports have appeared concerning the incidence of ulcers after the deprivation of pancreatic juice. Ivy and Fauley[8] found lesions in six of sixty-one animals after ligation of the pancreatic ducts. I found no changes in the stomach or duodenum in five dogs twenty-three, forty-seven, fifty-three, eighty and ninety-seven days after ligation. Dragstedt[9] observed no delay in the healing of experimental gastric ulcers or the formation of new ones in ten dogs after ligation of the minor pancreatic duct and transplantation of the major duct into the lower part of the ileum. In four dogs with pancreatico-ureteral anastomosis which had existed for sixteen, twenty-seven, thirty-four and thirty-seven days, respectively, and in one with a fistula of thirty-two days' duration Loewy[5b] found no duodenal ulceration after the prolonged loss of pancreatic juice. On the other hand, Elman and Hartmann[10] reported the occurrence of defects in the mucosa of the duodenum in all the animals of a series of six dogs with pancreatic fistulas of from thirteen to eighteen days' duration. These investigators attributed the lesions in the duodenum to the loss of the neutralizing effect of pancreatic juice on gastric acidity and minimized the importance of bile as a factor in the development of peptic ulcers in dogs.

In a series of eight depancreatized dogs which I examined sixty-one, seventy-eight, one hundred and thirty, one hundred and fifty-six, two hundred and twenty-three, two hundred and twenty-five, two hundred and fifty-eight and two hundred and seventy days after complete pancreatectomy the stomach and duodenum were normal.

The following observations were made on a series of sixteen dogs which were deprived completely of pancreatic juice by means of fistulas made according to the technic of Rous and McMaster, as adapted by Elman and McCaughan.[11] The daily ration of food, which consisted of the standard laboratory diet, was supplemented by sodium chloride administered intravenously in physiologic solution or in 5 per cent solution by stomach tube. Two dogs (36 and 58) received no additional sodium chloride, but showed a spontaneous adjustment of serum elec-

8. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine; Susceptibility of Jejunum to Ulcer Formation; Effect of Diet on Healing of Acute Gastric Ulcer, Am. J. Surg. **11:** 531 (March) 1931.

9. Dragstedt, C. A.: Unpublished observations communicated to the author.

10. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23:**1030 (Dec.) 1931.

11. Elman, R., and McCaughan, J. M.: Collection of Entire External Secretion of Pancreas Under Sterile Conditions and Fatal Effect of Total Loss of Pancreatic Juice, J. Exper. Med. **45:**561 (March) 1927.

trolytes, which will be described in detail in another paper. Although the administration of electrolytes prolonged the lives of the animals, all lost weight and after varying periods exhibited signs of profound metabolic disturbances. At postmortem examination the livers showed degenerative changes [12] consisting essentially of fatty infiltration and necrosis of the hepatic cells. The lesions varied in severity in different animals and were frequently accompanied by numerous dilated bile canaliculi. There was no obstruction of the extrahepatic bile ducts. Complete autopsies were performed on all of the animals, and histologic studies of the tissues were made. The presence of accessory pancreatic

Results of Deprivation of Pancreatic Juice in Sixteen Dogs Studied

Dog	Days of Secretion	Average 24 Hour Output of Pancreatic Juice, Cc.	Ulcers	Comment
152	12	200	0	
140	14	700	0	
153	14	300	0	
70	16	275	0	Multiple superficial mucosal erosions
89	18	200	0	
17	20	200	0	
147	20	250	0	
53	20	450	0	
49	20	300	0	Multiple superficial mucosal erosions; jaundice
156	22	225	0	
29	23	385	0	
52	25	600	+	Peritonitis due to two perforated duodenal ulcers; jaundice
36	25	300	0	
154	27	650	0	
58	31	400	0	
103	37	300	0	Jaundice

ducts and recommunication of the pancreatic duct system with the intestine were ruled out by careful dissections post mortem. The results with respect to the occurrence of ulcers and other conditions are presented in the accompanying table.

RESULTS

Analysis of the results shows that in only one instance (dog 52) were definite ulcers encountered after the loss of pancreatic juice. In this dog there were two perforated duodenal ulcers, which gave rise to diffuse peritonitis. It is interesting to note that this animal was one of three in which jaundice developed in association with marked degenerative changes in the liver.

In two animals (dogs 70 and 49) multiple small superficial erosions of the gastric and duodenal mucosa were found. I do not include such lesions within the category of ulcers, because similar changes are found in dogs under a variety of circumstances, viz., excessive vomiting, severe intoxications, infections, uremic poisoning and bilateral suprarenalectomy and as a terminal phenomenon. Until more is known concerning

12. Berg, B. N., and Zucker, T. F.: Liver Changes After Deprivation of External Pancreatic Secretion, Proc. Soc. Exper. Biol. & Med. **29**:68 (Oct.) 1931.

the etiology and development of ulcers, I believe that it is better, especially in experimental studies, to restrict the term "ulcer" to defects which involve one or more muscular layers as well as the mucosa and which correspond to the acute or chronic penetrating or perforating lesions that are encountered in man. This will diminish the confusion which exists concerning the interpretations of the results of different investigators due to the fact that no distinction is made between simple erosions and ulcers.

In some instances marked congestion of the mucosa of the duodenum and upper part of the jejunum was present.

COMMENT

My results tend to indicate that the absence of neutralization of gastric acidity by alkaline secretions, such as pancreatic juice, is not an important factor in the production of experimental peptic ulcers in dogs. This fits in with the observations of those [13] who found that gastric acidity is regulated by such factors as variations in the rate of secretion of hydrochloric acid, the amount of neutralization of the acid by bases in the mucus and food, the degree of dilution of the gastric contents, gastric motility and pyloric function, rather than by the regurgitation of alkaline duodenal fluids.[14]

Despite the fact that I employed a larger number of animals than Elman and McCaughan and that the periods of drainage were in many instances longer, the incidence of ulcers in my series of dogs was much lower than in theirs. The absence of lesions in completely depancreatized dogs which were deprived of their external pancreatic secretions for much longer periods of the time than the animals with fistulas constitutes further important evidence against the rôle of pancreatic juice in experimental ulcer formation.

In an earlier investigation [2] it was suggested that alterations in hepatic function other than the secretion of bile might be factors in the etiology of experimental peptic ulcers. Recently, Ivy, Schrager and Morgan [7] reintroduced this possibility and stressed the importance of jaundice and hepatitis in the development of ulcers in dogs with varying degrees of biliary obstruction. However, the livers of dogs deprived

13. (*a*) MacLean, H., and Griffiths, W. J.: The Automatic Regulation of Gastric Acidity, J. Physiol. **66**:356 (Dec. 20) 1928. (*b*) McCann, J. C.: Studies on the Control of the Acidity of the Gastric Juice, Am. J. Physiol. **89**:483 (Aug.) 1929. (*c*) Hollander, F., and Cowgill, G. R.: Studies in Gastric Secretion; Gastric Juice of Constant Acidity, J. Biol. Chem. **91**:151 (April) 1931. (*d*) Bolton, C., and Goodhart, G. W.: Mucus Factor in Automatic Control of Acidity of Gastric Contents, J. Physiol. **77**:287 (Feb.) 1933.

14. Boldyreff, W.: Self Regulation of Acidity of Gastric Contents and Real Acidity of the Gastric Juice, Quart. J. Exper. Physiol. **8**:1 (April 14) 1914.

of external pancreatic secretions often show marked degenerative changes,[13] although ulcers develop in only a small percentage in my experience. As present knowledge concerning the significance of pathologic changes in the liver with respect to function is limited, and as it is evident that the exclusion of bile or pancreatic juice is not a simple, isolated, experimentally induced deficiency, but involves many other complicated functional derangements, the interpretation of the mechanism underlying the tendency for peptic ulcers to develop under one set of conditions and not under others had better be deferred.

CONCLUSIONS

In a series of sixteen dogs deprived of pancreatic juice by means of fistulas for periods ranging from twelve to thirty-seven days, duodenal ulcers developed in only one animal. This animal was jaundiced and had marked degenerative changes in the liver.

In eight animals no ulcers were found in the stomach or duodenum from sixty-one to two hundred and seventy days after complete pancreatectomy.

The preponderance of evidence indicates that peptic ulcers develop more readily in dogs after the exclusion of bile than after the loss of pancreatic juice.

CHANGES IN THE BONE IN HODGKIN'S GRANULOMA

LLOYD F. CRAVER, M.D.

NEW YORK

AND

MURRAY M. COPELAND, M.D.

BALTIMORE

The bone marrow is more frequently involved in Hodgkin's granuloma than is suspected, as is shown by autopsy records. Ziegler found the marrow involved in 40 per cent of the cases, while Symmers noted medullary changes in 7 of 15 cases. These authors observed a proliferation of endothelial cells, fibrosis and, in some areas, an increase in normal cell elements of the bone marrow. Other changes characteristic of Hodgkin's granuloma were present.

Actual destruction of the bone has been reported from time to time with and without roentgenographic evidence. Since the advent of the roentgen rays, groups of cases are available in which the earlier symptoms referable to the bones together with the roentgenograms can be studied, and the progress of the disease followed to its termination.

CLINICAL STUDY

Of 396 cases registered as Hodgkin's granuloma in the Memorial Hospital, the diagnosis was found to have been confirmed by biopsy or at autopsy in 172. There were demonstrable changes in the bone in 27 cases (15.7 per cent) in this group. With the exception of 1 case, the changes were demonstrated prior to the termination of the disease.

The incidence of disease of the bone in this group of cases may be compared with that reported by the authors in table 1.

Of peculiar interest is the variable duration of Hodgkin's granuloma before and after definite invasion of the bone. In 12 persons changes occurred within two years after the onset of symptoms (table 2), while in 15 the disease was evident from two to four years before the changes in the bone. At the time this report was written, 11 patients were living with changes which had existed from four months to three years. In the patients who died, skeletal changes were noted from two months to two years prior to death.

A short clinical course prior to involvement of the bone did not necessarily presage rapid termination of the disease; neither did a long clinical course preceding invasion of the bone insure the patient against rapid and fatal termination of the disease. In some persons in whom

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changes in the bones developed from one to two years after the onset of the disease the subsequent clinical course was at least equal to the interval prior to evidence of osseous changes.

The age incidence did not vary from that found in the general group of patients with Hodgkin's granuloma. The greatest age incidence was found between 17 and 40 years. The age extremes were 17 and 57 years. The ratio of males to females was about equal, and in this respect the sex incidence varied from that found in cases without involvement of the bone. In the latter group the ratio of males to females was 2.3 : 1.

Pain preceded demonstrable invasion of the bone in 17 cases. It was of a dull aching or severe and lancinating quality. It was produced either by invasion of the nerve roots, by pressure on the nerve or by the destruction of the bone. Pain was frequently referred from the lumbar region to the lower extremities, and was accentuated by changes in posture. Girdle pains were experienced with vertebral changes.

TABLE 1.—*Incidence of Osseous Changes in Hodgkin's Granuloma as Reported by Various Investigators*

	Number of Cases	Cases with Osseous Change	Per Cent
Baldridge and Awe	46	6	13.0
Uehlinger, 1933	50	17	34.0
Barron	24	5	20.8
Kimpel and Belot	33	4	12.1
Dresser	149	16	10.7

The interval between the beginning of pain and the demonstration of osseous changes extended from a few days to three years and ten months.

The record of 7 cases gave insufficient data to estimate the relationship of pain to invasion of the bone.

In many cases roentgenograms of the affected bones were made periodically, and only after a considerable time had elapsed were changes in the density of the bone noted. Frequently bones without symptoms and totally unsuspected of being diseased showed roentgenographic changes. This emphasizes the importance of complete skeletal studies in estimating the incidence of invasion of the bone by Hodgkin's granuloma.

In 1 patient (case 1) pain was present in the back for a year prior to death. Roentgenograms repeatedly gave negative results. Five months prior to death the right rectus muscle became paralyzed. At autopsy marked destruction was found in the spongy bone of the vertebrae (fig. 1). Not infrequently pain with rigidity of the spine and localized tenderness were observed, associated with vertebral changes.

Signs of compression of the cord have occurred, associated with pain. In a few instances this was noted before roentgenologic evidence pointed to vertebral change (cases 3 and 23). In 5 patients (cases 5, 6, 17 and 18) compression of the cord was observed from three weeks to two years following the appearance of changes in the bone.

The signs of compression of the cord were: weakness of the extremities below the level of compression, paraplegia, anesthesia along
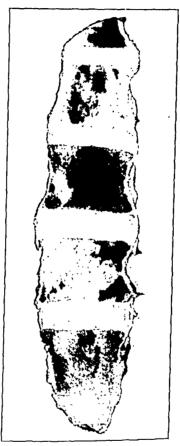
Fig. 1 (case 1).—Photograph of the lumbar vertebrae removed at autopsy and bisected. It is to be noted that the intervertebral disks are intact, showing no evidence of destruction. The bodies of the vertebrae show isolated and confluent patches of Hodgkin's granuloma invading the spongiosa of the bone. There is no periosteal reaction.

the distribution of the affected nerve and hyperesthesia about the hips or shoulder girdle associated with varying degrees of numbness in the distal portions of the extremities. Occasionally atrophy of the muscles was present. Spastic paralysis was an early feature in many of the cases.

Roentgen therapy was effective in ameliorating the spinal symptoms.

In case 8 a lesion of a rib was found by routine roentgenographic examination two months before pain and swelling were observed.

Osseous changes were found by roentgenographic examination following the clinical evidence of tumor in the bones in 2 cases. In both

Fig. 2 (case 8).—A photomicrograph showing active Hodgkin's granuloma invading the haversian canal of a rib. Note the activity of the disease. Endothelial giant cells are present in large numbers. Many plasma cells and eosinophils are seen. There is no evidence of fibrosis. The bone shows erosion with no tendency to the formation of new bone.

instances the interval between the appearance of swelling and the making of roentgenograms was due to the tardiness of the patient in coming under observation.

In 2 patients (cases 14 and 16) herpes zoster appeared on the left side of the chest during the course of the disease. In neither patient were lesions demonstrated in the thoracic vertebrae, but both had large mediastinal masses of nodes. The cause of herpes zoster has been variously ascribed to an impingement on nerves, to infiltration of the nerves by the disease or to toxic substances reaching the nerves by circulatory paths (Voorhoeve).

Abdominal pain (cases 5, 11 and 17) led to examination of the gastro-intestinal tract. The pain proved to be referred. It arose from
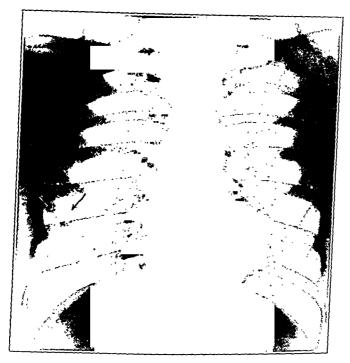
Fig. 3 (case 8).—A roentgenogram depicting a cystlike area of destruction in the right sixth rib. Note the central area of destruction with trabeculations. There is some periosteal proliferation.

diseased vertebrae impinging on the nerves, or from large retroperitoneal nodes disturbing the function of the stomach.

Retroperitoneal nodes frequently cause great distortion in the viscera by displacing them, often interfering with the normal function of the gastro-intestinal tract. It must be emphasized, however, that in some cases Hodgkin's granuloma actually invades the gastro-intestinal tract, especially the stomach, ileum and cecum (Craver and Haagensen). The following case is an example of Hodgkin's granuloma invading both gastro-intestinal viscera and bone.

CASE 8 (table 2).—*Autopsy.*—The body of E. N., a white youth, aged 21, was well developed but emaciated. There was no rigor mortis. The body was deeply

jaundiced. Small purpuric spots were seen over the chest and the abdomen. There was a beginning decubitus ulcer over the buttocks.

Chest: The heart, by request, was not disturbed, but the external appearance was that of acute dilatation. The pleural layers were distended with yellow, gelatinous edema. Old fibrous adhesions bound down both lungs. A moderate amount of straw-colored fluid was obtained from both pleural cavities. The lungs showed gelatinous edema throughout. No large bronchial nodes were observed. No tubercles were found in the lungs.

Abdomen: The peritoneum was edematous in its dependent portion. The mesentery of the small bowel contained three hard, yellowish calcified nodes, presumably old tubercles. The nodes along the aorta from above the celiac axis and for a short distance along the iliac vessels were all enlarged and filled with granulomatous tissue. The bulk of the disease was found in the upper part of the abdomen where there was extension into the nodes about the head of the pancreas, the bile duct and both suprarenals. The spleen weighed 480 Gm. It was of a deep purplish color and on section showed areas typical of Hodgkin's granuloma. The liver was large, bile-stained and filled with granulomatous tissue in solitary and confluent patches. The stomach showed scattered areas of Hodgkin's granuloma in the prepyloric segment. The kidneys and bladder were normal. The testicles were atrophied.

Bones: The right sixth rib appeared involved. The upper lumbar vertebrae showed hyperplastic marrow, but no positive evidence of granuloma. The marrow of the femurs was hyperplastic.

Microscopic study revealed Hodgkin's granuloma of a cellular type involving the retroperitoneal, perigastric and pancreatic nodes and the liver, spleen and stomach. Old healed calcified and fibrosed tubercles were found in the mesentery. The bone marrow of the vertebrae and femurs showed mucinous degeneration without evidence of granuloma. The rib was involved. The granulomatous process infiltrated the haversian canals and extended beneath the periosteum (figs. 2 and 3). The periosteum showed an osteoplastic reaction much like that seen in Ewing's tumor (Ewing).

CONSTITUTIONAL REACTION

The temperature varied in no particular from that found in the larger group of cases without known lesions of the bone. Fever accompanied by a slight albuminuria, was frequently associated with the disease, especially in its active phase. Though a search for Bence-Jones bodies in the urine was not a routine procedure, they were not found in the cases in which the tests were performed (cases 2, 7, 13 and 24). Several tests were made in some of the cases. Galloway reported the presence of a Bence-Jones-like protein in the urine of a patient with Hodgkin's granuloma, whose kidneys were involved. No mention was made of the condition of the bone marrow.

The blood picture ranged from a normal blood count to one showing marked secondary anemia. The white cell count varied from one showing leukopenia to a count showing marked leukocytosis. A detailed analysis of the trend in the blood picture is complicated by the effects of repeated irradiation on the blood-forming tissues. In general a moderate to severe secondary anemia was frequently found.

TABLE 2.—*Data on Twenty-Seven Cases of Hodgkin's Granuloma*

Case	Age	Sex	Duration of Disease Prior to Osseous Change	Symptoms Related to Osseous Changes (Before and After Roentgenographic Evidence)	Demonstrable Visceral and Glandular Involvement	Osseous Involvement*	Microscopic	Treatment of Bones	Laboratory Findings	Duration of Life Following Osseous Change
1	34	M	4 yrs., 4 mos.	Pain 1 yr. before; paralysis of right rectus muscle 5 mos. before	Left side of neck, left supraclavicular nodes, axillae, groins, mediastinum, retroperitoneal nodes, liver, spleen	Right femur, diffuse (O); lumbar vertebrae 1, 2, 3, 4, 5 (C)	Hodgkin's granuloma, fibrotic	Mixed low and high voltage roentgen therapy, 12/7/26 to 12/30/30	Progressive secondary anemia	Dead; changes found at autopsy
2	40	M	3 yrs., 1 mo.	Pain in bone 1 yr. before; spine rigid 1 yr. before	Right cervical node, left axilla, both groins, mediastinum	Thoracic vertebrae 11, 12 (O); lumbar vertebra 1 (O); after treatment (B)	Hodgkin's granuloma, cellular	High voltage roentgen therapy, 4/26/30 to 10/2/30	Moderate secondary anemia; Bence-Jones bodies negative	Living after 3 yrs.
3	34	M	4 yrs.	Pain 10 mos. before spinal change; flaccid paralysis 2 mos. before	General glandular enlargement; spleen palpable	Thoracic vertebrae 11, 12 (B); lumbar vertebra 1 (B)	Hodgkin's granuloma	Radium emanation pack; high voltage roentgen therapy, 8/22/28 to 10/16/28	Marked secondary anemia	Dead after 4 mos.
4	45	F	8 yrs., 10 mos.	Pain 3 yrs., 10 mos. before; rigidity of spine 6 mos. after	Bilateral cervical nodes, lateral right breast, left axilla, right groin, retroperitoneal nodes	Lumbar vertebrae 2, 3, 4 (B), with transverse processes (O); lumbar vertebra 3, partial collapse; left sacro-iliac region (B)	Hodgkin's granuloma, sarcomatous	Roentgen therapy, 6/20/28 to 12/3/30	Slight leukocytosis; normal red blood count and hemoglobin	Lost after 2 yrs., 5 mos.
5	57	M	2 yrs.	Pain 2 wks. before; abdominal pain 7 mos., 2 wks. before; intestinal symptoms 5 mos. before; signs of cord compression 4 mos. after	Right axilla, right and left cervical nodes, inguinal regions, retroperitoneal nodes attached to vertebrae, mediastinum	Thoracic vertebra 9 (C), with collapse; sacrum (O); left 6th rib (O); pathologic fracture	Hodgkin's granuloma, cellular	Roentgen therapy	Progressive secondary anemia	Dead after 7 mos.
6	17	F	5 yrs., 4 mos.	Pain 2 mos. before; signs of cord compression 2 yrs., 1 mo. after; rigidity of spine 1 yr., 2 mos. after	Left supraclavicular nodes, suprasternal notch, mediastinum, groin	Cervical vertebra 6 (O); lumbar vertebrae 2, 3, 4 (O), with collapse; lumbar vertebra 5 (B); transverse process of lumbar vertebrae 3, 4, 5 (O); right 12th rib (O)	Hodgkin's granuloma	Radium therapy, 4/17/22 to 12/14/26; radium emanation pack, 5/15/26 to 5/28/26	Marked secondary anemia	Dead after 3 mos.

7	17	F	1 yr., 4 mos.	Pain in lumbar region 7 mos. before; signs of cord compression 6 mos. after	Left and right cervical nodes, axillae	Lumbar vertebrae 1, 2, 3 (O); transverse process of lumbar vertebra 3 (O); left ilium near crest (O); right and left sacroiliac joint regions (O); right midilchium (O)	Hodgkin's granuloma	High voltage roentgen therapy, 1/4 S.E.D. to 3/2; ...	Moderate sever, duty amemia and leukopenia. Done. ... positive	Living well 1 yr. 4 mos.
8	21	M	9 mos.	Pain; tumor 2 mos. after	Bilateral cervical nodes, right axilla, spleen, retroperitoneal nodes, liver, stomach, periaortic pancreatic node	Right 6th rib (t and B)	Hodgkin's granuloma, orbital	High voltage roentgen therapy, ...	Progressive	[illegible]
9	27	F	2 yrs., 10 mos.	Unsatisfactory data	Bilateral cervical nodes, axillae	Thoracic vertebrae 8, 9 (t), with col lapse	Hodgkin's granuloma, orbital	High voltage roentgen therapy, ...	...	[illegible]
10	26	F	3 yrs., 7 mos.	Unsatisfactory data	Bilateral cervical nodes, axillary, inguinal and mediastinal nodes	Thoracic vertebra 12 (t); lumbar vertebrae 1, 2, 3 (t), with collapse; osteoblastic reaction about collapsed area	Hodgkin's granuloma	High voltage roentgen therapy, ...	...	[illegible]
11	32	M	1 yr., 6 mos.	Unsatisfactory data	Left cervical nodes, mediastinum, right cervical nodes, axillae	Right ilium, mid. portion (O); left ilium near sacro iliac margin (O); area along acetabular area involved	Hodgkin's granuloma	High voltage roentgen therapy, ...	Moderate ...	[illegible]
12	41	M	2 yrs.	Unsatisfactory data	Right and left supraclavicular nodes, axillae, mediastinum	Lumbar vertebra 3 (B) with transverse process (O); sacroiliac (B) near sacro iliac joints; right ilium central (O); left ilium central (O)	Hodgkin's granuloma	High voltage roentgen therapy, ...	...	[illegible]
13	20	M	1 yr., 2 mos.	Pain 1 yr., 3 wks. before	Left cervical nodes, axillae, over left clavicle and right scapula	Frontal bone (O); lumbar vertebrae 1, 2, 3, 4, 5 (B)	Hodgkin's granuloma	High voltage roentgen therapy, ... S.E.D. ...	Moderate, ... Hemo... ...	[illegible]

* Osteoclastic involvement is indicated by (O); osteoplastic, by (B).
† S.E.D. indicates skin erythema dose.

Improvement in the anemia followed irradiation of the diseased bones or lymph nodes, unless the marrow received a dose of roentgen therapy which temporarily inhibited the formation of blood. Osseous involvement did not materially alter the blood picture from that generally seen in the disease.

Leukocytosis was often observed during the course of the disease. The differential count of the white blood cells showed polymorphonuclear neutrophils ranging from 38 to 90 per cent. In 20 cases, from 1 to 6 eosinophils were observed in individual blood counts. Leukopenia, when present, usually followed substantial irradiation. A leukocytosis was often reduced to a relatively normal level by irradiation. The treatment causing a reduction in the white blood cells was not always directed toward the osseous system. The terminal phases of the disease revealed a progressive emaciation and anemia.

OSSEOUS INVOLVEMENT

A review of the literature [1] indicates that vertebral changes are most frequent. The bones involved in the order of their frequency were: vertebrae, sternum, pelvis, femur, ribs, skull, humerus, scapula and clavicle. Few reports dealt with lesions of other bones.

Among our own patients the bones most constantly affected were those of the spine and pelvis (table 3 and fig. 4). Pathologic fracture was rare. In cases 5 and 22 a rib was fractured. In case 22 partial collapse existed in the head of the left humerus together with fracture.

Collapse of the diseased vertebrae was commonly observed (table 2).

Roentgen Studies.—The osseous lesions as depicted by roentgenograms were either predominantly osteoplastic (fig. 5) or osteoclastic (fig. 6). In the long pipe bones the involved portion was usually situated near the proximal end. As the disease progressed, the entire bone was frequently involved. When one considers that Hodgkin's granuloma appears early in the hematopoietic tissues, the reason for this distribution of osseous invasion becomes apparent. Piney, in 1922, made an anatomic and histologic analysis of the bone marrow. He found that at birth all of the skeleton except the cranium contained red marrow. As the person's age increased, fatty deposits replaced the marrow gradually. In the adult, the vertebrae, sternum and pelvis and most of each rib contained red marrow. The only red marrow in the long bones was found at the upper ends of the diaphyses.

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1. The review of the literature includes all the bibliography with the exception of the references to: Copeland and Geschickter, Ewing, Craver and Haagensen, Galloway, Piney and Voorhoeve.
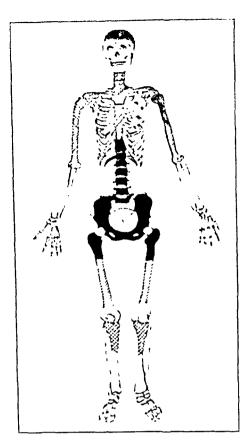
Fig. 4.—Diagram showing the distribution of Hodgkin's granuloma in the skeleton. The black areas represent the most frequent sites of invasion; the checkered areas, the common sites of involvement; the diagonal lines, the occasional areas invaded, and the white areas, the rarely invaded portions of the bones.

TABLE 3.—*Involvement of Bone in Twenty-Seven Cases of Hodgkin's Granuloma*

	Number of Cases	Number of Times	Right	Left
Vertebrae				
Cervical 6	1	1	..	..
Thoracic 8	1	1	..	..
Thoracic 9	2	2	..	..
Thoracic 10	1	1	..	..
Thoracic 11	4	4	..	..
Thoracic 12	4	4	..	..
Lumbar 1	8	8	..	..
Lumbar 2	9	9	..	..
Lumbar 3	7	7	..	..
Lumbar 4	7	7	..	..
Lumbar 5	7	7	..	..
Pelvis				
Ilium	7	12	6	6
Ischium	3	4	3	1
Pubis	2	3	2	1
Sacro-iliac joint	2	3	1	2
Sacrum	2	2	..	..
Femur				
Upper third	2	3	2	1
Mid third	3	3	1	2
Lower third	1	2	1	1
Humerus				
Upper third	2	3	1	2
Mid third	1	1	..	1
Tibia (upper third)	2	3	1	2
Ribs 1	2	1	1	..
2	2	2	1	1
3	1	1	1	..
4	1	1	1	..
6	3	3	1	2
12	1	1	1	..
Skull				
Frontal bone	2	2	..	..
Parietal bone	1	1	..	..
Sternum (lower third)	1	1	..	..

A progression of the disease was found to accentuate further the two varieties of osseous change already mentioned. In many cases destruction of bone and the production of new bone accompanied each other.
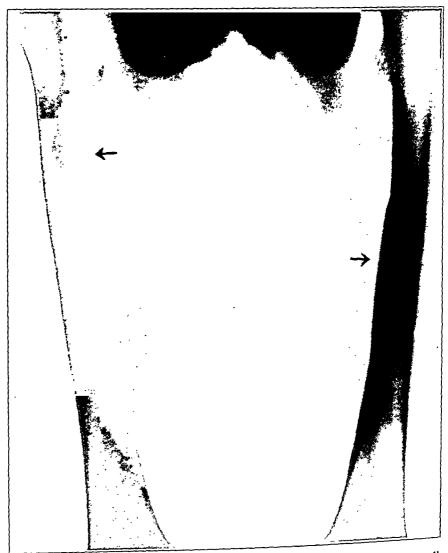
Fig. 5 (case 19).—A roentgenogram showing Hodgkin's granuloma invading both the left and the right femurs. The lesions of the left femur simulated Garré's osteomyelitis with thickening of the cortex, a proliferation of the periosteum and a tendency to obliterate the marrow cavity. The right femur in its upper portion shows a small area of central destruction with some thickening of the medial cortex and a slight periosteal reaction about the area of involvement.

Roentgenograms of the skull in this series presented a predominant osteoclastic reaction. The areas of destruction were surrounded by varying degrees of increased density, representing new bone.

Involvement of the larynx with extension to the cartilage has been reported (Askanazy, 1931). We have not seen such an invasion by Hodgkin's granuloma.

In case 25, the sternum, a bone in close approximation to involved mediastinal nodes, showed a marked periosteal reaction (fig. 7) with cortical destruction of the bone and with little tendency to the formation of new bone.

Fig. 6 (case 12).—Roentgenogram of the left ilium showing a central area of destruction. In the distal portion of the ilium small areas of destruction are seen with areas of increased density about them. These areas suggest an overlying lymph node affected by Hodgkin's granuloma infiltrating directly into the bone. The areas of increased density represent an attempt on the part of the bone to wall off the disease process.

The lesions in the rib in all instances appeared much like metastatic processes with marked destruction. In case 8 (fig. 3), when first observed in the roentgenograms the lesion appeared much like a cyst of the bone.

There was marked central destruction with a periosteal reaction and the formation of new bone which appeared like a shell about the diseased bone.

The vertebrae either showed complete destruction with partial collapse or appeared sclerosed, with or without collapse. Sclerosis of the
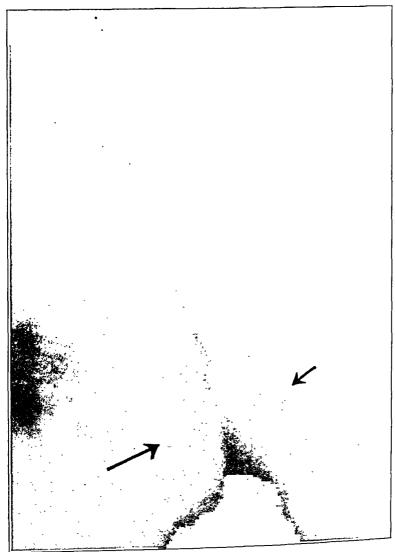
Fig. 7 (case 25).—Roentgenogram showing invasion of the lower portion of the sternum by Hodgkin's granuloma. There are periosteal proliferation and cortical destruction with practically no formation of new bone. Many of these cases represent direct infiltration from mediastinal nodes involved by the disease.

vertebral bodies and osteolytic changes in the transverse processes were often depicted in the same roentgenogram. As many as three or four vertebrae were found partially collapsed, one on the other, giving the

appearance of one or two diseased vertebrae rather than four (fig. 8). Dresser, who has made a study of this feature, found that the intervertebral disks were intact despite the fact that the bone was destroyed about them. Uehlinger found that the intervertebral disks were sometimes crushed and broken. In some instances the disks showed step formation due to peculiarities of osseous destruction.
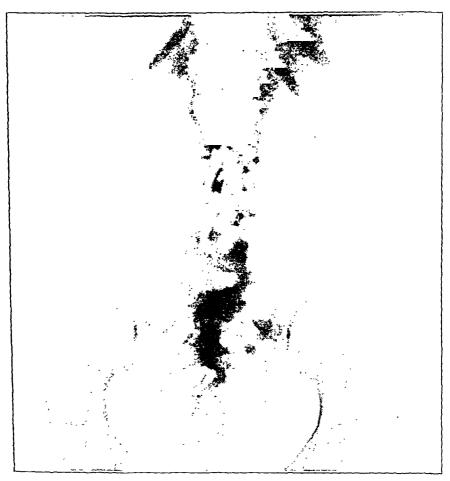
Fig. 8 (case 7).—Roentgenogram showing marked destruction of the third and fourth lumbar vertebrae. Partial collapse of the vertebrae is noted. Periosteal proliferation together with some formation of new bone is seen. There is increased density of the fifth lumbar vertebra. The transverse processes of the fifth lumbar vertebra show osteolytic involvement.

The periosteum of the vertebrae was frequently raised. The subperiosteal proliferation varied in amount and was often associated with collapse of the vertebrae.

Evidences of spinal osteo-arthritis were occasionally observed, and while not a specific expression of the disease process, the osteophytes formed were involved occasionally by Hodgkin's granuloma (fig. 9). In case 4 the first roentgenograms revealed only the features of an osteo-arthritis with marked lipping of the vertebrae. Later roentgeno-
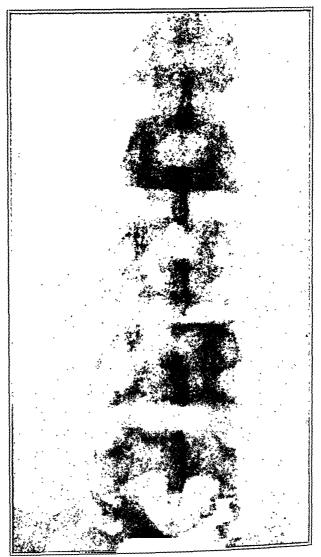
Fig. 9 (case 18).—Roentgenogram of the lumbar spine showing evidences of osteo-arthritis about the second, third and fourth lumbar vertebrae. The second and fourth lumbar vertebrae show increased density with some areas of rarefaction. The bridging process between the vertebrae may become involved by the disease.

grams demonstrated a bridging process between the third and fourth transverse processes of the lumbar vertebrae. In the center of this bony bridge an area of destruction was seen. Still later films revealed marked destruction of the third and fourth lumbar vertebrae.

The pelvis, lying in close proximity to lymph nodes, frequently showed combined sclerotic and osteolytic features. The majority of lesions appeared in the wings of the ilia or about the sacro-iliac joints. Osteolytic areas were surrounded by areas of increased density (fig. 6). The acetabula were less frequently involved than was expected.

In the long bones, such as the humerus, a destructive area appearing in the upper end of the bone just beneath the periosteum was common.
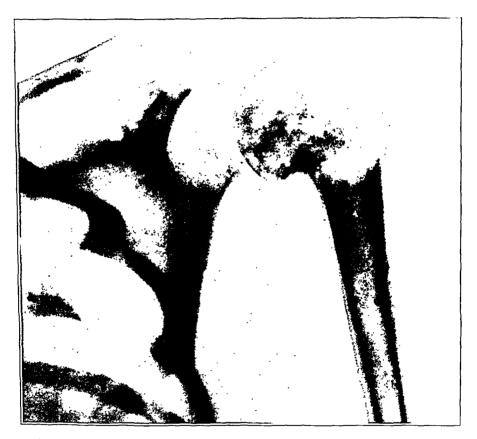
Fig. 10 (case 22).—Roentgenogram showing marked destruction of the head of the humerus. Note the pathologic fracture and partial collapse. Below the area of destruction small areas of rarefaction may be seen in the shaft. The periosteum is lifted by the disease process and gives an appearance somewhat similar to the onion-peel formation frequently seen in Ewing's tumor.

Infiltration was the rule, causing partial collapse of the diseased bone with fracture (fig. 10). The disease infiltrated beneath the periosteum, lifting it from the cortex. A central destructive process involving the cortex was often seen (fig. 11). Some lesions simulated Garré's non-

suppurative osteomyelitis (fig. 5). The cortex was thickened with or without small foci of rarefaction. A definite periosteal proliferation was present and blended with the cortical thickening. The earliest osseous change found was either a slight increase in the density or a porosity of the entire bone. The earlier changes were difficult to establish as definite involvement of the bone.
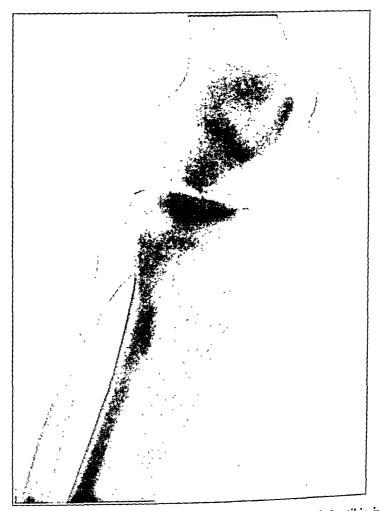
Fig. 11 (case 14).—Roentgenogram showing the upper end of the tibia involved by a central destructive process. Areas of increased density may be seen around the areas of destruction. The entire upper end of the tibia shows rarefaction.

GROSS MATERIAL AND MICROSCOPIC EXAMINATION

In all cases under observation biopsies of the cervical, axillary or inguinal nodes were done. Complete autopsy was performed in 2 cases. In case 1 (fig. 1) the diseased lumbar vertebrae were obtained, and on cross-section showed discrete and confluent patches of Hodgkin's granuloma, the process infiltrating the spongy bone of the vertebrae.

No periosteal reaction was seen. The intervertebral disks were not involved. In case 8 (figs. 2 and 3) one rib showed a lifting of the periosteum with proliferation of granulomatous tissue beneath it. On bisection, the rib showed a central destructive area with some reactive bone about it. Granulomatous tissue beneath the periosteum coalesced with the reactive bone. The marrow from the vertebrae and femur of the same case showed mucinous degeneration but no evidence of Hodgkin's granuloma. The marrow in the rib near the lesion was in large part replaced by the granulomatous process. In the more remote portions of the rib the marrow was hyperplastic.

A histopathologic study of the lymph nodes showed changes varying from those of Hodgkin's granuloma with marked fibrosis (case 1) to those of Hodgkin's granuloma with sarcomatous features (case 5). The greater number of the cases showed a cellular granuloma with a moderate number of endothelial giant cells, proliferation of endothelium infiltration by eosinophils and some plasma cells. Varying degrees of fibrosis were noted. Unfortunately, the biopsy specimens usually were not taken at the time the lesions of the bone were first observed. It is therefore impossible to estimate the activity of the disease at the time the bone was involved. In case 1 invasion of the bone was noted at autopsy and yet could not be demonstrated in the roentgenograms. In this case the Hodgkin granuloma was of the fibrotic type. In case 16, in which histopathologic changes were of a similar type, osseous changes in the rib were easily demonstrated roentgenographically and proved to be osteolytic.

It is evident from the duration of the disease before and after the changes in the bone that its activity varied in different patients. It is noteworthy that histopathologic studies may show varying degrees of activity in different tissues of the same patient.

Of importance is the fact that where diseased lymph nodes lie in close approximation to the bones there is often found a direct extension from the nodes to the bone. This is seen especially about the sternum, vertebrae and pelvis. The changes in the bone, however, do not seem to be altered because of a different mode of involvement.

DIFFERENTIAL DIAGNOSIS

Hodgkin's granuloma affecting bone may be confused with metastatic deposits in the bone from carcinoma, neoplastic processes such as lymphosarcoma and the leukemias. Ewing's tumor may be simulated during certain phases of the osseous invasion. Less frequently the condition has been confused with various forms of osteomyelitis, including Garré's osteomyelitis. In one case a lesion of the rib had many of the characteristics of a cyst of the bone.

A careful physical examination of the patient will do much to obviate mistaken diagnosis.

Varying degrees of involvement of the lymph nodes, with enlargement of the spleen, itching and secondary anemia, are characteristic of Hodgkin's granuloma. A biopsy is made with little difficulty in the majority of cases.

Metastatic carcinoma as a rule shows central destruction of bone without the production of new bone. A periosteal reaction is usually lacking. In two types of metastases to the bone, however, an osteoplastic reaction may predominate, i. e., in metastases from the prostate and the breast. Such reactions are more apt to be confused with Hodgkin's granuloma.

Lymphosarcoma may cause similar changes in the bones. A biopsy is of great importance in distinguishing between the two diseases. The spleen is less likely to be involved in lymphosarcoma, and many of the constitutional symptoms of lymphogranuloma are absent.

The leukemias are discovered by studies of the blood. A routine examination of the blood should be made in cases in which there are osseous lesions. The bones may show only osteoporosis in the roentgenogram, or osteoplastic features may predominate, with or without periosteal reaction. These features of osseous invasion are often seen in Hodgkin's disease.

In osteomyelitis, adenopathy and enlargement of the spleen are lacking. The leukocyte count may be of value if it is high. It is to be remembered, however, that in Hodgkin's granuloma a moderate leukocytosis is frequently present and rarely there may be a marked leukocytosis. A sequestrum with a shaggy periosteal reaction characterizes the usual case of osteomyelitis. In atypical osteomyelitis a biopsy may be necessary to establish its identity. Garré's nonsuppurative osteomyelitis has been simulated by Hodgkin's disease (fig. 5). The other features of the disease should serve to distinguish it from nonsuppurative osteomyelitis.

<center>TREATMENT</center>

Despite valuable adjuncts, such as heliotherapy, a regimen such as is given in tuberculosis, large doses of arsenic, transfusions and the experimental use of various serums, filtrates or avian tuberculin, the main reliance in the treatment of Hodgkin's disease continues to be on irradiation, with either gamma or roentgen rays, preferably the latter in most cases.

Various methods of irradiation have been suggested and tried by different workers. Some irradiate with single heavy doses; others prefer protracted fractional irradiation. Some follow a routine of irradiation of nearly all the lymph node-bearing areas, regardless of demonstrable implication in the disease process; others have contented themselves with treating on a purely symptomatic basis.

In general, it appears that patients do not tolerate well a routine heavy irradiation of all the lymph node areas, and, on the other hand, failure to secure satisfactory palliation in the past has often been due to neglect of treatment of certain areas such as those containing the deeper nodes. In recent years at the Memorial Hospital we have employed almost exclusively high voltage roentgen rays, either in suberythema or in fractional doses, depending on the local and general condition of the patient, and have paid much more attention than formerly to the treatment of the mediastinal and retroperitoneal regions, when there was demonstrable or presumable involvement of those areas. No routine dosage is applied. Each case is individualized. The treatment regarded as best is that which will secure the best palliation for the longest time. The treatment should never be so severe as to make it seem harder to bear than the disease. The skin should be spared severe reaction. In the last two years we have found Heublein's method of prolonged continuous low intensity irradiation of the entire body to be a valuable part of the treatment in a number of cases.

The gross lesions of the bones may be treated to good advantage either by single large suberythema doses or by fractional doses of high voltage roentgen rays. Relief from pain is often prompt, and reparative processes may be demonstrated in some cases. In the terminal stages, however, we do not attempt routine irradiation of all the bones, although it is well known that the marrow is usually diffusely involved, as in such cases a severe degree of anemia and sometimes leukopenia already exists and would only be aggravated by irradiation.

SUMMARY

1. One hundred seventy-two patients with Hodgkin's granuloma, proved histologically, have been studied.

2. Twenty-seven patients (15.7 per cent) were found to have involvement of the bone.

3. The bones most frequently involved were found to be those of the spine and pelvis.

4. Pathologic fracture was found to be rare, but collapse of the vertebrae was frequent.

5. Two types of osseous changes were noted: osteoplastic and osteolytic. A combination of both was seen in many cases.

6. Two routes of osseous involvement may be assumed: (1) from the marrow foci of Hodgkin's granuloma; (2) from the contiguous diseased lymph nodes from which direct infiltration into bone occurred.

7. The intervertebral disks were rarely involved.

8. No relationship between the structure of the lymph nodes and the type of osseous change could be demonstrated.

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A CLEAN INTESTINAL ANASTOMOSIS

AN EXPERIMENTAL STUDY

EDGAR J. POTH, Ph.D., M.D.
Fellow in Medicine of the National Research Council

SAN FRANCISCO

The question of intestinal anastomosis has been attacked by numerous workers, and a tremendous literature has accumulated. Among the more recent workers, Halsted [1] published a paper in 1922 describing his blind-end circular suture, which acted as a great stimulus to investigations pertaining to the technic of intestinal suture. In 1922 Horine [2] stated that 217 methods had been suggested for performing intestinal anastomoses. Since his review, 58 additional publications bring the total to 275 proposals.

Naturally there are many duplications, and in general the suggested technics or methods can be classified under two main heads: the open method and the closed method. The stimulus for much of the work has been to find a so-called aseptic technic. Strict asepsis, from the surgical point of view, probably cannot be attained consistently. Technics affording a minimum of soiling have been devised, but there are factors other than contamination governing success or failure. An important and obvious factor is the size of the stoma at the site of anastomosis immediately after the operation as well as during the months to follow. The fear of temporary obstruction following the end-to-end anastomosis prevents its more frequent application. Much of the immediate obstruction is due to edema of a traumatized, inverted cuff at the line of suture. In the following procedure a minimum amount of tissue is inverted without crushing and without impairment of circulation.

PROCEDURE

The course of the operation is readily followed from the diagrams, supplemented by a few details as to the successive steps. The segment of bowel to be removed is freed, the mesentery is divided and unshod and noncrushing, intestinal clamps

1. Halsted, W. S.: Blind-End Circular Suture of the Intestine, Ann. Surg. 75:356, 1922.

2. Horine, C. F.: Aseptic Technic for the Resection of the Intestine, Ann. Surg. 76:745, 1922.

are placed across the viscus (fig. 1). The bowel is divided with a cautery between the clamps, leaving about 0.5 cm. beyond each clamp so as to prevent the intestine from slipping out of the loose blades. After placing a purse-string suture of linen about 2 mm. from the edge of each clamp as indicated in figure 1B, the first posterior row of half-mattress sutures of fine black silk are introduced as close to the purse-string sutures as possible. Care must be taken to place all sutures in the same order, i.e., to begin each suture by taking a bite to include the submucosa, so that the exit of the needle from the wall of the bowel will be nearer the mesenteric border than its entrance, while the subsequent bite in the opposite section
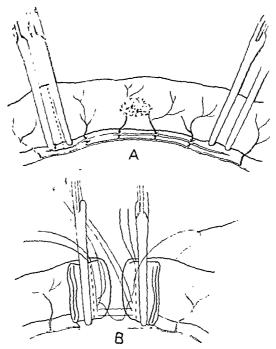
Fig. 1.—*A*, a segment of the bowel with the intestinal clamps in place for the division of the viscus with a hot cautery; *B*, the divided bowel with the two linen purse-string sutures placed and the first posterior row of anastomosing sutures being introduced.

of the viscus will be taken in the reverse order, so that the exit of the needle will be distal and its entrance proximal to the mesenteric border of the intestine. This is readily followed by tracing out the course of a single suture in figure 1B. If this precaution is not observed in placing the sutures, difficulties will be met in approximating the edges later. The ends of these sutures are tied together and placed in safety-pins, which in turn are threaded onto another pin as illustrated in figure 2. When the sutures are secured by the safety-pins, it is impossible to tangle them. In introducing the first anterior row of sutures, one begins at the mesenteric border of the intestine and observes the same precautions in placing them as in the case of the posterior row. In addition, the thread bridging between the two segments of bowel is carried around the ends of the occluding clamps as shown in figure 3.
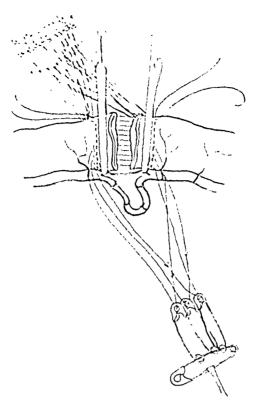
Fig. 2.—The first posterior row of sutures in place and the introduction of the first anterior row of anastomosing sutures; all of the anastomosing sutures are secured in safety-pins.
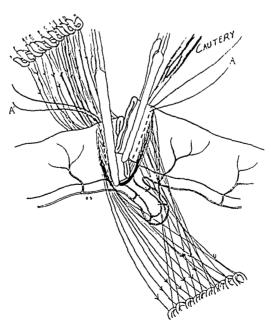
Fig. 3.—All of the first row of anastomosing sutures are in place, the bowel is lifted by the intestinal clamp and the area between the clamp and the purse-string suture *A* is cleared, ready for the removal of the intestinal cuff beyond the clamp. The edge of the clamp acts as a guide for the hot cautery.

With completion of the entire first row of sutures, the operator raises the end of one segment of bowel by grasping the intestinal clamp and smooths down the sutures with physiologic solution of sodium chloride, so that they will not lie in the area between the linen purse-string suture and the intestinal clamp but will rather "umbrella" down the sides of the intestine. This precaution is taken so as not to damage these structures in the subsequent division of the bowel. The
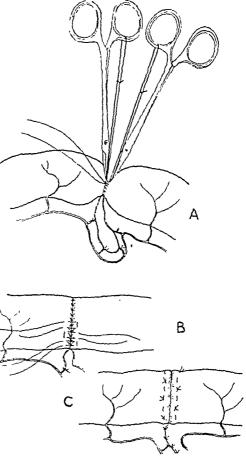
Fig. 4.—The approximation of the ends after removing the intestinal cuffs and pulling up the anastomosing sutures: *A,* all of the sutures of the first row are tied except the final ones before cutting the purse-string sutures against the jaws of the securing mosquito clamps; *B,* the first row is completed, and the purse-string sutures are released with the opening of the lumen of the bowel and the introduction of a second row of sutures; *C,* an illustration of the complete anastomosis, using the Halsted mattress suture in the second row of anastomosing sutures.

cuff of bowel beyond the purse-string sutures is to be resected by division of the bowel with a hot cautery against the clamp and beyond the purse-string sutures. After placing a first knot in the purse-string suture, an assistant pulls the suture taut at an angle of approximately 45 degrees with the intestinal clamp, so as not

to come in contact with the hot cautery, as the bowel is closed simultaneously with its division. The cautery is directed across the bowel against the jaws of the intestinal clamp, which thus determines the line of section and insures against damage to the sutures. The purse-string sutures are pulled up just tight enough to prevent leakage from the lumen of the bowel, but not enough to interfere with free bleeding from the larger vessels in the visceral wall. These vessels are clamped with small Halsted clamps and tied with fine silk. Usually three bleeding vessels will be found: two in the proximal·segment and one in the distal segment of the bowel. Without placing a second knot in the purse-string sutures, they are secured with small Halsted clamps as illustrated in figure 4*A*.

The cauterized ends are approximated, the intervening slack in the anastomosing sutures is taken up by pulling each suture individually, and all but two of the sutures are tied. Then the purse-string sutures are cut close to the jaws of the securing clamps, the clamps are removed and the remaining two anastomosing sutures are tied. The bowel will remain constricted until massaged or forced open with axial pressure, when it will open out to its normal diameter. A second row can be laid down, using either a Halsted mattress suture, as shown in figure 4*B*, or a continuous Cushing stitch, as the operator chooses.

Obviously this technic can be applied to end-to-side and side-to-side anastomoses. This has been done readily and without other than self-evident modifications. It might be worth while to mention that no leakage occurs when the bowel is distended markedly with water after completion of the first line of sutures.

RESULTS

Once the entire technic was established, no deaths which could be attributed to the method occurred in forty-five successive operations. One animal died on the fifth postoperative day and showed bilateral pneumonia, one died on the ninth day of distemper, and another animal was killed by other dogs on the twelfth postoperative day. None of these animals had peritonitis, and the line of anastomosis showed normal healing. A stitch abscess was found in one animal killed on the tenth day following a second anastomosis done on the sigmoid flexure of the same animal ten days after the first operation.

Three series of twelve operations each were carried out on the sigmoid flexure: (1) first row, interrupted half-mattress sutures of fine black silk; second row, Halsted mattress sutures of fine silk; (2) first row, interrupted half-mattress sutures of fine black silk; second row, continuous sutures of fine black silk; (3) a single row of Halsted mattress sutures of fine black silk, placed after the ends of the bowel had been divided and closed by the purse-string sutures. In each series, specimens were taken immediately, six, twelve and twenty-four hours and two, three, five, seven, ten, fifteen, twenty and twenty-five days following the operation, and the condition of the abdominal cavity and stoma of the viscus was noted.

Whether or not the lumen of the bowel was patent was determined in the following manner: The gas in the bowel on one side of the anastomosis was milked out, and if the bowel was immediately refilled

by gas from the loop of viscera across the line of anastomosis, the lumen was considered patent. These conditions were fulfilled in all cases except three in the third series in which a single row of Halsted mattress sutures was placed after the ends of the bowels were closed with the purse-string sutures. In this series the bowel was found to be occluded on the third, fifth and seventh days. Opening of the bowel showed the lumen to be occluded by the edematous inverted shelf. Naturally, it would have been possible to bring about the same conditions in the other two series by turning in large amounts of tissue when placing the second row of sutures. But, as will be indicated later, the
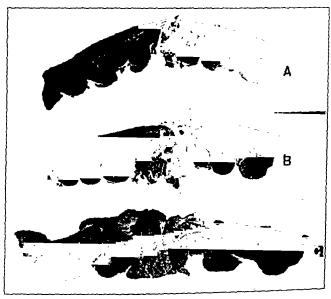
Fig. 5.—Sections taken immediately following the suture (all from the same segment of bowel): *A*, a cross-section with the first row of sutures placed; *B*, same as *A*, plus a second row of continuous sutures; *C*, same as *A*, plus a second row, using the Halsted mattress suture.

shelf is determined by the amount of tissue turned in with the second row of sutures and is under the absolute control of the operator.

Subsequently, in another series of experiments, nine end-to-end anastomoses were done on the small bowel using the technic employed in series 1 with consistently good results.

Practically all of the publications following the communication of Halsted [1] dealt with various methods of releasing the purse-string sutures of the blind ends so as to remove the diaphragm. No contributions were made which would lead to reduction in the amount of inverted viscus or to more accurate placing of the anastomosing sutures. In all

cases except Holman's [3] "presection" method the purse-string suture was tied down before the bowel was divided, or before the anastomosing sutures were placed. In the technic presented here, the anastomosing sutures are accurately placed directly against the purse-string sutures and not more than 2 mm. from the inverted end of the bowel. Furthermore, the sutures are placed while the bowel is held between clamps, so that corresponding portions of the bowel's cross-section are readily and accurately approximated.

No crushing clamps are applied to the intestine, so the opportunity for soiling by squeezing organisms through the visceral wall is mini-
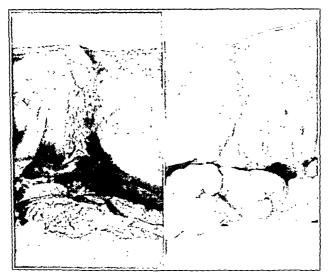
Fig. 6.—Two specimens removed four months after anastomosis in the sigmoid flexure.

mized. The 2 mm. or less of inverted cuff has not been crushed and should show but slight trauma or devitalization. The operation recommended by Parker and Kerr,[4] using the "basting stitch," turns in a crushed and traumatized cuff of bowel, whereas, if the procedure described here is followed, there is no palpable thickening at the line of anastomosis when the lumen of the bowel is reestablished following the completion of the first row of sutures (fig. 5 *A*). Therefore a second row of sutures may be applied. And it is not necessary to limit the sutures to the smallest possible bites. They are rather placed so as

3. Holman, Emile: End-to-End Anastomosis of the Intestine by Presection Sutures, Bull. Johns Hopkins Hosp. **31**:300, 1920.

4. Parker, E. M., and Kerr, H. H.: Intestinal Anastomosis Without Open Incision by Means of Basting Stitches, Bull. Johns Hopkins Hosp. **19**:132, 1908.

to turn in the amount of lumen which will provide the extent of approximation of the serosa desired by the operator (fig. 5). For all practical considerations the shelf at the line of anastomosis depends on the tissue turned in by the second row of sutures, and this is under the direct control of the surgeon.

Obviously, this procedure can be interrupted at any stage by dividing the bowel, tying the purse-string sutures and performing an enterostomy. Also, it is noteworthy that from the time the intestinal clamps are placed until after completion of the entire first row of sutures the viscera need not be handled directly. So long as the intestinal clamps are in place, the bowel can be manipulated from the handles of these instruments. After they have been removed, the Halsted clamps on the purse-string sutures may be used to approximate the blind ends.

The method has the disadvantages of any technic employing interrupted sutures in that it requires more time than is necessary when continuous sutures are used, but experience shows that it requires no more time than any other method in which interrupted sutures are used. The maze of untied sutures (fig. 3) must appear hopeless at first glance, but if they are handled as outlined and placed on safety-pins, no difficulties will be encountered. This method of dealing with numerous untied sutures should find application in other procedures in which the same conditions are met.

SUMMARY

1. A clean technic is described for closed intestinal anastomosis in which the trauma and soiling are reduced to a minimum and the amount of inverted cuff is under the direct control of the operator.

2. A method for handling many untied sutures is suggested.

3. A novel procedure is given for the simultaneous division and occlusion of the bowel between the clamp and purse-string suture.

4. The results of forty-five experimental operations are reviewed.

PATHOLOGIC FRACTURES OF THE SPINE ASSOCIATED WITH DISORDERS OF CALCIUM METABOLISM

BARCLAY W. MOFFAT, M.D.

NEW YORK

The occasional report in the literature of pathologic fractures of the spine as a result of the loss of calcium associated with tumor of the parathyroid glands seems to have given rise to the impression that this is a rare and strange condition. It is my purpose to point out that pathologic fractures resulting from the loss of calcium from the spinal column are not uncommon and are, in the majority of cases, due to a faulty diet. In a previous article,[1] six cases were analyzed to determine the changes in the intervertebral disk associated with this condition. In four of these six cases the condition was due to faulty diet. I shall present in outline four additional cases and a description of this condition as a definite clinical entity.

CLINICAL OBSERVATIONS

The typical clinical course starts with fatigue referred to the spine, usually with some accentuation of the anteroposterior curves. This condition increases in severity, and usually before the patient consults an orthopedic surgeon he has subjected the spine to sudden strain. This is followed by a sharp pain localized in its greatest intensity and usually accompanied by pains radiating along the spinal nerve roots, indicating that a fracture has taken place. In one of the cases presented, this pain occurred when the patient stooped over to pick an object off the floor. In the most severe case, one of those included in the aforementioned article,[1] the patient sustained additional fractures from simply turning in bed. On examination there is tenderness throughout the affected portions of the spine over the spinous processes. Even when no fracture has occurred, the diagnosis rests on roentgenographic observations, which are described in later paragraphs.

Age.—The age of the patient at the time of the onset apparently is not a factor in this condition. The youngest patient was 18, and the oldest, 68 years of age.

Etiology.—The etiologic factor is necessarily a condition in which either the normal amount of calcium is not taken from the intestinal tract or an abnormal amount is being excreted. The skeleton is the storing place of calcium in the body, and that contained in the spinal column seems to be more mobile than that stored in other bones. That this is the case appears likely when one considers the cancellous structure of the vertebral body and its rich supply of blood. In only one instance did roentgen examination show the rest of the skeleton to be deficient in calcium.

Considering the first of the two causes: There may be either an insufficient calcium content in the food or a local condition in the intestinal tract interfering with the passage of calcium through the intestinal wall. In regard to the quantity of calcium in the food, it should be pointed out that this nation as a whole subsists on the absolute minimum intake of calcium compatible with health. It is not surprising, therefore, that the diet drops below this minimum in a great number of persons. The second factor concerning the intake of calcium includes an alkaline condition in the intestinal tract causing the formation of insoluble salts and the presence of fatty acids which bring about the saponification of calcium with consequent excretion of these insoluble materials. A lack of vitamin D also inhibits passage of calcium into the circulation.

In by far the greater proportion of cases the fault lies in the intake of calcium. In cases of abnormal excretion of calcium, the endocrine glands are most often at fault. The parathyroid glands regulate the output of calcium, that is, hyperactivity of a parathyroid gland results in an outpouring of calcium from the skeleton by way of the alimentary and urinary tracts. Though the fact is not yet generally recognized, the pituitary gland is also concerned with the metabolism of calcium. A tumor of either the pituitary or a parathyroid gland, therefore, may result in the condition which I describe.

Roentgenographic Observations.—The roentgenographic observations are characteristic. In the earlier cases it is not always possible to demonstrate the presence of osteoporosis, inasmuch as the density of the spinal shadow in the x-ray picture may vary with the differing thicknesses of the patient's body and with the technic of the roentgenologist. The earliest constant sign is a change in the shape of the intervertebral disk, which takes on a more pronounced biconcave form and at times becomes completely spherical. This is due to hypertrophy, as shown in the article to which I have referred.[1]

The rapidity of the onset may also be judged by the presence or absence of condensation of bone at the upper and lower margins of the vertebral body. When the condition is slowly progressive, the white line will be apparent, indicating that the body has had time to strengthen its wall against the pressure of the hypertrophied disk. The process

is similar to that which occurs in smaller areas of the margins of the body in the case of extravasation of the contents of the nucleus pulposus, in which the same line of condensed bone is found at the bottom of an indentation, marking the site of the break in the envelop of the nucleus.

Fractures, when they occur, are compression fractures, and it is characteristic that they are not accompanied by extravasation of the contents of the disk with a consequent lessening of its height, as are

Fig. 1.—Roentgenogram of the spine in a case of loss of calcium; an early stage of the process is shown.

fractures occurring in normal vertebral bodies in which the trauma is necessarily greater.

REPORT OF CASES

CASE 1.—R. R., a woman, aged 27, complained of fatigue in the back without cause in March, 1932. This became worse. In February, 1933, she experienced a sudden sharp pain in the lower dorsal region while performing an exercise which consisted of touching the floor with her legs which were extended above her head while she was lying in the supine position. The pain radiated about the trunk following the course of the spinal nerve roots. A roentgenogram (fig. 1) was taken

on March 18, 1933, and shows osteoporosis of the bodies, slight increase in the height of the intervertebral disks and condensation of bone at the upper and lower margins of the bodies. There is a compression fracture of the tenth dorsal vertebra with slight angulation of the spine at this portion. The condition is in an early stage and of slow onset.

CASE 2.—L. L., a woman, aged 68, complained of fatigue in the back over a period of years previous to my seeing her, which she ascribed to age and for which she did not seek treatment until, in stooping to pick an article from the floor, she experienced a snapping sensation in the back accompanied by severe pain

Fig. 2.—Roentgenogram of the spine in a case of loss of calcium in which the changes are more advanced.

and collapse. The roentgenogram (fig. 2) shows the same condition as in the previous case but in a more advanced state. The biconcave appearance of the disks, the osteoporosis and the condensation of the margins are more marked. There is a compression fracture of the twelfth dorsal and first lumbar vertebrae.

Determination of the Calcium Balance.—The calcium balance indicated dietary deficiency. The daily diet supplied 0.558 Gm. of calcium. The amounts of calcium excreted in the urine were as follows: July 18 (volume of urine, 645 cc.), 0.227 Gm.; July 20 (volume, 785 cc.), 0.283 Gm.; July 23 (volume, 600 cc.), 0.190 Gm.

From July 18 to July 20 the feces (moist weight, 150 Gm.; dry, 24.6 Gm.) contained 0.542 Gm. of calcium. The total intake of calcium for July 18 and 19 was 1.116 Gm.; the total amount excreted was 1.010 Gm.; the gain in calcium was 0.106 Gm.

On July 21, the feces (moist, 395 Gm.; dry, 42 Gm.) contained 0.427 Gm. of calcium. The total intake of calcium was 0.558 Gm.; the total amount excreted was 0.661 Gm.; the loss in calcium was 0.103 Gm.

On July 22, the feces (moist, 380 Gm.; dry, 27 Gm.) contained 0.589 Gm. of calcium. The total intake of calcium was 0.558 Gm.; the total amount excreted was 0.823 Gm.; the loss in calcium was 0.265 Gm.
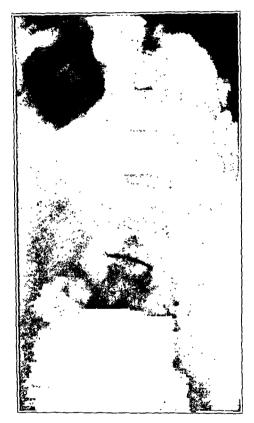
Fig. 3.—Roentgenogram of the spine showing a compression fracture of the twelfth dorsal vertebra.

On July 23, the feces (moist, 445 Gm.; dry, 26 Gm.) contained 0.154 Gm. of calcium. The total intake of calcium was 0.558 Gm.; the total amount excreted was 0.344 Gm.; the gain in calcium was 0.214 Gm.

On July 20, the blood calcium was 11.4 Gm. and the blood phosphorus 3 mg. per hundred cubic centimeters.

CASE 3.—H. W., a woman, aged 59, complained of fatigue in the back over a period of four years, with marked increase in local pain following a fall. A roentgenogram (fig. 3) taken in March, 1932, shows the same condition as in the previous cases with compression fracture of the twelfth dorsal vertebra.

CASE 4.—C. F., a woman, aged 48, complained of fatigue in the back over a period of several months. There was an onset of sharp pain following an attempt to lift a patient out of bed. The roentgenogram (fig. 4) shows the same condition as in the previous cases with compression fracture of the ninth and twelfth dorsal vertebrae.

Determination of Calcium and Phosphorus Balances.—The calcium and phosphorous balances indicated dietary deficiency. The daily diet was varied. On July 29, 1932, the report on the feces was: total weight, 35 Gm.; moisture, 73 per cent; dry weight, 9.5 Gm.; calcium, as Ca, 0.160 Gm.; phosphorus, as P, 0.061 Gm.

Fig. 4.—Roentgenogram of the spine showing compression fractures of the ninth and twelfth dorsal vertebrae.

The report on the urine was: volume, 1,200 cc.; calcium, as Ca, 0.028 Gm.; phosphorus, as P, 0.105 Gm. The intake of calcium in the diet was 0.535 Gm.; that of phosphorus, 0.943 Gm. The gain in calcium was 0.347 Gm.; in phosphorus, 0.777 Gm.

On July 30, the report on the feces was that there had been none. That on the urine was as follows: volume, 1,480 cc.; calcium, as Ca, 0.028 Gm.; phosphorus, as P, 0.878 Gm. The intake of calcium in the diet was 0.556 Gm.; that of phosphorus, 1.235 Gm. The gain in calcium was 0.528 Gm.; in phosphorus, 0.357 Gm.

On July 31, the report on the feces was: total weight, 1,100 Gm.; moisture, 94.3 per cent; dry weight, 62.7 Gm.; calcium, as Ca. 0.546 Gm.; phosphorus, as

P, 1.826 Gm. The report on the urine was: volume, 700 cc.; calcium, as Ca, 0.065 Gm.; phosphorus, as P, 0.372 Gm. The intake of calcium in the diet was 0.554 Gm.; that of phosphorus, 1.230 Gm. The loss in calcium was 0.057 Gm.; in phosphorus, 0.968 Gm.

On August 1, the report on the feces was: total weight, 40 Gm.; moisture, 76 per cent; dry weight, 9.6 Gm.; calcium, as Ca, 0.150 Gm.; phosphorus, as P, 0.077 Gm. The report on the urine was: volume, 1,400 cc.; calcium, as Ca, 0.051 Gm.; phosphorus, as P, 0.826 Gm. The intake of calcium in the diet was 0.550 Gm.; that of phosphorus, 1.215 Gm. The gain in calcium was 0.349 Gm.; in phosphorus, 0.312 Gm.

TREATMENT

The first requisite is, of course, the determination of the causes in the particular case. Evidences of pituitary disorder should be searched for, and the sugar tolerance test should be carried out. Parathyroid disorder may sometimes be diagnosed only by elimination of other possible factors, though in some cases a palpable tumor of one of these glands is present. The calcium and phosphorous balances should be worked out to eliminate the alimentary factor. In the case of tumor of a parathyroid gland, the treatment is necessarily removal of the gland. In the case of alimentary deficiency the patient should be given calcium gluconate and increasing doses of viosterol. The back should be supported with a brace rather than with a plaster cast, and the patient should be kept out of bed. The reason for these measures is, of course, to prevent further loss of calcium from disuse.

CONCLUSIONS

1. Loss of calcium from the spinal column presents a definite clinical picture.

2. This condition may be diagnosed and a prognosis given by definite roentgenographic signs in the early stages, when the process may be easily checked.

3. Pathologic fractures commonly result in the later stages.

4. In the majority of cases the diet is at fault, and only rarely is the faulty metabolism of calcium due to tumor of the pituitary or parathyroid glands.

333 East Forty-Third Street.

TOXEMIA IN ACUTE INTESTINAL OBSTRUCTION

TOXICITY OF INTESTINAL CONTENTS, WITH SPECIAL REFERENCE TO THE PANCREATICODUODENAL SECRETION

W. D. GATCH, M.D.

H. M. TRUSLER, M.D.

AND

R. E. LYONS, JR., M.D.

INDIANAPOLIS

In general, the experimental studies on the causes of death in acute intestinal obstruction have resulted in a tangle of conflicting opinions. The work of Haden and Orr [1] on the significance of chemical changes in the blood threw a new light on the problem, and this led to a series of investigations [2] which in part offer an explanation for the lack of agreement in previous experimental work. It is now generally conceded that the issue is clarified by a recognition of two fundamental types of intestinal obstruction: (1) simple obstruction and (2) strangulation. In simple intestinal obstruction in which there is no interference with the circulation of the intestinal wall, the chief cause of death is the metabolic disturbance resulting from the loss of fluids and electrolytes. Obstruction, however, is practically always complicated by damage to the intestine from overdistention or strangulation. Although the importance of dehydration and alkalosis must always be considered, there are other factors even more important. Frequently gangrene of the bowel and peritonitis are grossly apparent causes of death. In many cases of obstruction, however, the death seems inexplainable, except on the basis of some undetermined factor which is assumed to be a specific toxemia.

The toxic substances which may be demonstrated in the contents of an obstructed bowel have been studied repeatedly. Much significance has been attached to the symptoms produced by injecting into animals the contents of obstructed intestinal loops. It has been assumed that

1. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**:365 (March) 1923; The Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog after Pyloric and Intestinal Obstruction, ibid. **38**:55 (July) 1923.

2. Gatch, W. D.; Trusler, H. M., and Ayres, K. D.: Acute Intestinal Obstruction Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, Am. J. M. Sc. **173**:649 (May) 1927.

these experiments constitute evidence concerning toxemia in intestinal obstruction; it has been assumed that the normal intestinal contents is for the most part innocuous,[3] and that a specific toxin is formed primarily as the result of obstruction. Here again, however, results and conclusions are controversial. We are reporting a series of investigations on this subject.

In this article it is our purpose to present the results of numerous tests on the toxicity of the contents of normal as well as obstructed intestine. We have collected the material from human subjects as well as from experimental animals. Many experiments of this type have been reported previously by other workers using various methods of investigation. Cooper[4] gave a complete bibliography of this work and elaborated on the extreme diversity of opinion concerning the toxicity of intestinal contents. It is obvious that results will vary according to the manner of preparing and testing such material, and this explains much of the controversy.

METHOD OF TESTING

This report includes only the results obtained by testing the material either in its crude state or modified by such simple procedures as centrifugation, filtering or autoclaving in preparation for intravenous injection. The criteria of toxicity we used are likewise simple. The tests include: (1) intravenous and intraperitoneal injection of the various preparations into dogs, rabbits and mice with observation as to death or toxic symptoms in the animals, and (2) kymographic record of the effects produced on the blood pressure by such injections into dogs under ether anesthesia.

The second method of study was particularly valuable in making comparative examinations of numerous samples. It also gave us information concerning the toxicity of many preparations difficult to evaluate by gross observation following their injection into normal animals. The dosage of the injection for dogs and rabbits varied from 1 cc. for each 5 Kg. to 5 cc. per kilogram of body weight. The small injections of 0.2 cc. per kilogram were extremely valuable in kymographic studies comparing the effects of various samples of material in the same animal. We found that in this dose preparations possessing any significant toxicity caused a sharp fall in blood pressure with a prompt return to normal. The injection was made at a uniformly rapid rate (approximately 0.5 cc. per second). With an extremely slow injection the response was less definite.

By such observations we can expect to demonstrate only the presence or absence of toxic substances. A study as to the possibilities of their

3. Ellis, J. W.: Cause of Death in High Intestinal Obstruction, Ann. Surg. **75**:429 (April) 1922.

4. Cooper, H. S. F.: The Cause of Death in High Obstruction, Arch. Surg. **17**:918 (Dec.) 1928.

absorption through the intestinal wall is being published separately. Further information obtained by chemical analysis also follows as a subsequent publication. As a basis for the discussion which follows we have made hundreds of tests. It is our aim to present sufficient data to demonstrate the facts. To display the entire investigation in detail is futile and unnecessary.

TOXICITY OF NORMAL INTESTINAL CONTENT

The normal contents of the bowel in dogs and in human subjects is always toxic when injected intravenously into animals. We wish to emphasize this fact because previous reports on the subject have seemed to conflict and have caused confusion. Davis and Stone [5] and also Dragstedt and his co-workers [6] reported the normal secretion of the intestinal mucosa to be innocuous when so collected as to be free from other substances. We confirmed this observation and have no reason to doubt it. The normal contents of the bowel, however, is an entirely different material and, even in the absence of food, will include gastric juice, bile and pancreatic juice in addition to the normal secretion of the intestinal mucosa. Nevertheless, the terms have been confused, and there is a widespread impression that the normal intestinal contents has little or no toxicity and becomes toxic directly only as the result of obstruction. This conception is a fallacy. It is true that marked changes occur in the intestinal contents as the result of obstruction, and these will be discussed later. In regard to the demonstration of toxic substances, however, our tests consistently showed the normal intestinal contents to be even more toxic than material removed from an obstructed bowel. We tested numerous samples of material collected from both small and large intestines of normal dogs under various conditions of feeding or fasting, filtrates from human feces, material promptly removed from the human small intestine at autopsy and drainage material from enterostomy in man. Though obviously there must be considerable variation in the constituents of such material, practically all the samples showed toxic properties causing depression in the blood pressure. To rule out the known toxic effect of intravenously injecting large numbers of bacteria or gross particulate matter we used Berkefeld filtrates (diluting the original sample with saline solution when necessary). Also for comparison we studied the original liquid samples as nearly unchanged as possible, merely centrifugating and injecting the supernatant fluid through a needle of 22 gage or less.

5. Davis, D. M., and Stone, H. B.: Studies on the Development of Toxicity in Intestinal Secretion, J. Exper. Med. **26**:687 (Nov.) 1917.

6. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: The Nature of the Toxemia of Intestinal Obstruction, Preliminary Report, Proc. Soc. Exper. Biol. & Med. **14**:17 (Oct.) 1916.
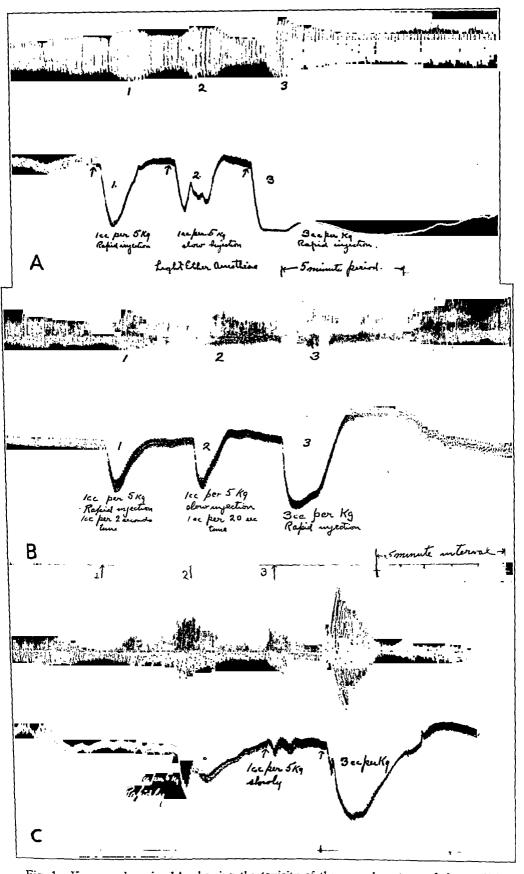
Fig. 1.—Kymograph series 1A, showing the toxicity of the normal contents of the small intestine of dogs on intravenous injection into a dog anesthetized with ether. The upper tracing shows the respirations; the lower, the blood pressure. The spaces between arrows indicate five minute periods. *A* was obtained following the injection of centrifugated supernatant fluid; *B*, following the injection of a Berkefeld filtrate; *C*, following the injection of autoclaved centrifugated supernatant fluid.

Tables 1 and 2 outline the results of such a series of tests. The toxic symptoms mentioned in all the tables are typically as follows: If the animal is a dog, the toxic injection is promptly followed by dyspnea, salivation, vomiting, defecation or tenesmus, micturition, muscular tremor and prostration. Following this severe reaction the animal

TABLE 1.—*Toxicity of Normal Contents of Small and Large Bowel in Dogs**

Test Animal	Material Injected	Intravenous Dose†	Result
Dog 485	Sample 1; contents of small intestine of normal dog; centrifugated supernatant fluid	3 cc.	Severe toxic symptoms; died in 20 hours
Dog 481	Berkefeld filtrate of sample 1..............	3 cc.	Mild toxic symptom; recovered
Dog 497	Sample 2; contents of small intestine of normal dog; centrifugated supernatant fluid	3 cc.	Severe toxic symptoms; died in 7 hours
Dog 496	Berkefeld filtrate of sample 2..............	3 cc.	Toxic symptoms; died in 48 hours
Dog 488	Sample 3; contents of small intestine of normal dog; contrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 30 min.
Dog 484	Berkefeld filtrate of sample 3..............	3 cc.	Toxic symptoms; recovered
Dog 575	Sample 4; contents of small intestine of normal dog; centrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 2 hours
Dog 571	Berkefeld filtrate of sample 4..............	3 cc.	Died in 2 hours
Dog 573	Sample 4, autoclaved and centrifugated....	3 cc.	Died in 10 hours
Dog 648	Sample 5; contents of large bowel of normal dog; material suspended in equal part of saline solution; centrifugated supernatant fluid	3 cc.	Mild toxic symptoms; recovered
Dog 642	Berkefeld filtrate of sample 5..............	3 cc.	Mild symptoms; recovered
Dog 644	Sample 5, autoclaved and centrifugated....	3 cc.	Mild symptoms; lived 10 days
Rabbit 28	Sample 6; contents of small intestine of normal dog; centrifugated supernatant fluid	5 cc.	Convulsions; immediate death
Rabbit 29	Berkefeld filtrate of sample 6..............	5 cc.	Died in 18 hours
Rabbit 70	Sample 7; contents of small intestine of normal dog; centrifugated supernatant fluid	5 cc.	Convulsions; immediate death
Rabbit 71	Berkefeld filtrate of sample 7..............	5 cc.	Convulsions; immediate death
Rabbit 23	Sample 8; contents of large bowel of normal dog; material suspended in equal part of saline solution; centrifugated supernatant fluid	5 cc.	Convulsions; immediate death
Rabbit 24	Berkefeld filtrate of sample 8..............	5 cc.	Recovered

* The term "normal" is used merely to indicate the absence of obstruction and ordinary conditions of feeding.
† Per kilogram of body weight.

usually dies in a few hours. If, however, the reaction is less drastic, as is often the case even with large doses, the dog frequently recovers completely. Rabbits behave in an entirely different manner. If the injection is extremely toxic, the rabbit promptly dies in convulsions. If death does not occur thus, the animal merely becomes prostrated and dies or recovers after a variable number of hours. Though rabbits are easily killed by injections containing particulate matter, they may tolerate in proportion to their weight even larger doses of Berkefeld filtrates than dogs do. The same is true of mice receiving intraperitoneal injections (doses of 1 and 2 cc.). These small animals would at first thought
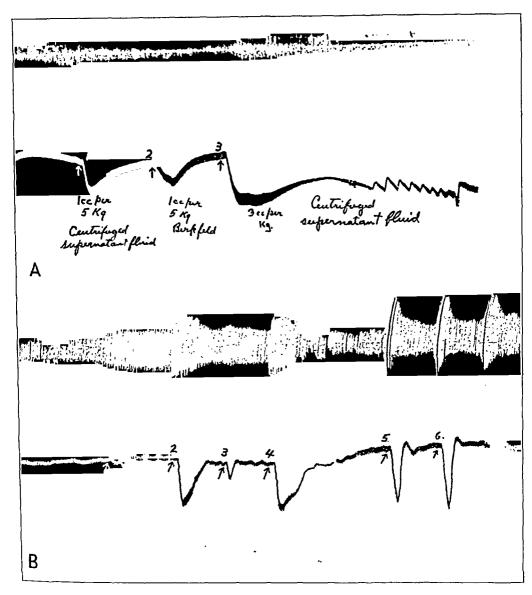
Fig. 2.—Kymograph series 1B, showing the results of tests on the normal content of the large intestine of dogs. The samples were suspended in equal parts of saline solution, and intravenous injections made into a dog anesthetized with ether. The spaces between the arrows indicate five minute periods. *A* was obtained following the injection of the normal contents of the large intestine of dogs. *B* shows the variation in toxicity of material from the large intestine of a dog as compared with the material from the small intestine of the same animal. All doses were 1 cc. for each 5 Kg. of body weight. The material injected was as follows: 1. Supernatant fluid, contents of large intestine, dog A; sample suspended in equal part of saline solution. 2. Supernatant fluid, undiluted contents of small intestine, dog A. 3. Sample from large bowel, dog B. 4. Sample from small bowel, dog B. 5. Sample from large bowel, dog C. 6. Sample from small bowel, dog C.

seem to be of value in detecting small amounts of these toxins. The few we have used have been so resistant as to offer little aid in this study. In general, we have not found intraperitoneal injection a satisfactory test. Though absorption by that route may often be sufficient to produce toxic symptoms or death in dogs, results are easily complicated by peritonitis when any of the more crude preparations are injected.

Of all the tests, the kymographic studies have been of greatest value. One might raise the objection that toxins could be present and yet

TABLE 2.—*Toxicity of Human Intestinal Contents in the Absence of Obstruction* *

Test Animal	Material Injected	Intravenous Dose†	Result
Dog 574	Sample 1; contents of human small intestine removed soon after death from apoplexy; centrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 30 minutes
Dog 576	Berkefeld filtrate of sample 1..............	3 cc.	Toxic symptoms; recovered
Dog 572	Autoclaved and centrifugated portion of sample 1	3 cc.	Toxic symptoms; recovered
Rabbit 10	Sample 2; contents of human small intestine removed soon after death from pneumococcic peritonitis; centrifugated supernatant fluid	5 cc.	Convulsions; died at once
Rabbit 8	Berkefeld filtrate of sample 2..............	5 cc.	Died in 16 hours
Rabbit 11	Autoclaved and centrifugated portion of sample 2	5 cc.	Died in 16 hours
Dog 641	Sample 3; human feces suspended in equal parts of saline solution; centrifugated supernatant fluid	3 cc.	Toxic symptoms; died in 7 hours
Dog 640	Berkefeld filtrate of sample 3..............	3 cc.	Mild toxic symptoms; recovered
Dog 643	Autoclaved and contrifugated portion of sample 3	3 cc.	Mild toxic symptoms; recovered
Dog 293	Drainage from enterostomy of upper jejunum, case 1; centrifugated supernatant fluid	3 cc.	Severe toxic symptoms; died in 24 hours
Dog 344	Enterostomy drainage, case 1; Berkefeld filtrate	3 cc.	Died in 2 days
Dog 296	Enterostomy drainage, case 1; autoclaved and centrifugated supernatant fluid	3 cc.	Recovered
Rabbit 83	Enterostomy drainage, case 1; centrifugated supernatant fluid	5 cc.	Died in 3 days
Rabbit 63	Enterostomy drainage, case 1; Berkefeld filtrate	5 cc.	Lived 4 weeks
Rabbit 78	Enterostomy drainage, case 1; autoclaved and centrifugated supernatant fluid	5 cc.	Lived 3 weeks

* Samples obtained from fresh autopsy material, suspension of feces in saline solution and enterostomy drainage.
† Per kilogram of body weight.

not be detectable on the kymographic tracing. However, repeated comparisons have demonstrated that any sample of intestinal material capable of producing toxic symptoms tends proportionately to exert a surprisingly characteristic depressant action on the blood pressure.

Berkefeld filtrates of the normal intestinal contents are much less toxic than the centrifugated supernatant fluid. Autoclaved preparations are similarly reduced in toxicity. Kymographic studies, however, show all these preparations to possess, even in small doses, a powerful though transient depressing action on the blood pressure. The large doses give an effect which is more prolonged and may or may not permit complete return to normal.
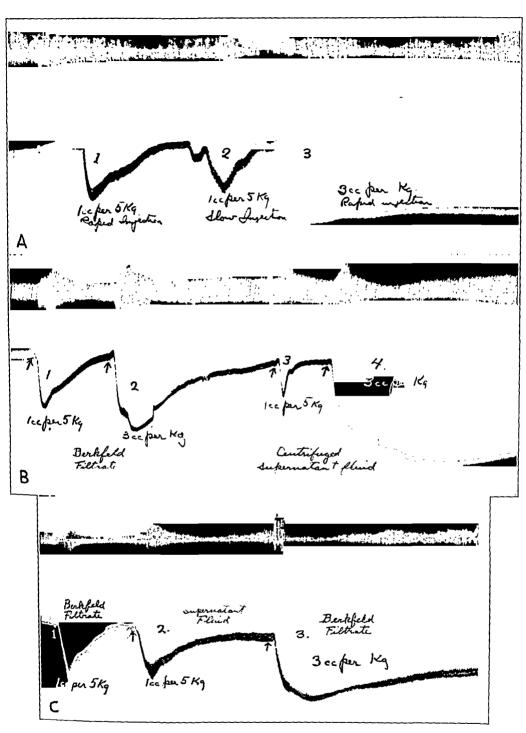
Fig. 3.—Kymograph series II, showing the results of tests on the normal contents of human intestine. Intravenous injections were given dogs under ether anesthesia. The upper tracings show the respirations; the lower, the blood pressure. The spaces between arrows indicate five minute periods. *A* was obtained following the injection of a Berkefeld filtrate of the normal contents of the small intestine (fresh autopsy specimen) ; *B*, following the injection of human feces suspended in saline solution (equal parts). *C* shows the toxicity of drainage material from a high enterostomy performed for relief of obstruction in a human subject.

Filtered suspensions of human feces and similar preparations of material from the large bowel of dogs are less toxic than material taken from the small intestine. At first thought this might be explained by the dilution necessary in making the liquid suspension of samples from the large bowel. One must admit, however, that the sample from the large bowel is a dehydrated residue of material formerly in liquid form in the small intestine.

Before discussing what possible significance these elementary facts may have in the study of intestinal obstruction, let us consider the sources of this toxic property. Products of protein degradation, bacterial toxins, bile or other digestive juices and all the heterogeneous products of digestion could be considered. Many of these and numerous other substances intravenously injected may cause a drop in the blood pressure and other symptoms similar to the reaction we have described. Further consideration of all these possibilities is unnecessary, however. The experiment outlined in table 3 demonstrates a salient fact.

TOXICITY OF THE PANCREATIC SECRETION

The pancreatic secretion as obtained from an isolated duodenal loop fistula is violently toxic when injected intravenously. The following experiment, one of several similarly performed, has enabled us to collect samples of material free from food, bile, gastric secretion and all other substances except pancreatic juice plus the secretions of the duodenal mucosa. This material is highly toxic when collected and tested fresh. Its toxicity is not materially altered by stagnation in the loop. Neither does it change appreciably on long standing in the refrigerator. The pancreatic juice alone as drained fresh from a cannula placed in the pancreatic duct likewise demonstrates a depressant action on the blood pressure. Though we have not completed our studies on this point, we have found thus far that the secretion so obtained is less toxic than the combined secretion of the pancreas and duodenum. In fact, samples collected from isolated duodenal loop fistulas possess toxicity equal to or greater than that of any material we have tested. Because of this observation we are impressed that any consideration of toxicity due to other products of digestion or bacterial putrefaction is of minor importance as concerns the study of normal intestinal contents. In the study of contents from obstructed bowel we must consider the various factors which modify the normal.

Protocol (Dog 264).—Food was withheld from a dog for forty-eight hours. Laparotomy was performed under ether anesthesia; the pylorus was sectioned and ligated and the stump inverted. The common bile duct was ligated and the gallbladder drained to the outside. The ligament of Treitz was divided sufficiently to permit a high gastrojejunostomy. The duodenum was sectioned just proximal to the gastrojejunostomy, and both stumps were inverted, the proximal duodenal

stump enclosing a short rubber tube which was brought through the abdominal wall. This tube drained freely the combined pancreaticoduodenal secretion. Tests on this material freshly collected were highly toxic as shown in kymograpic record III (fig. 4). Additional toxicity tests are shown in table 3. The animal
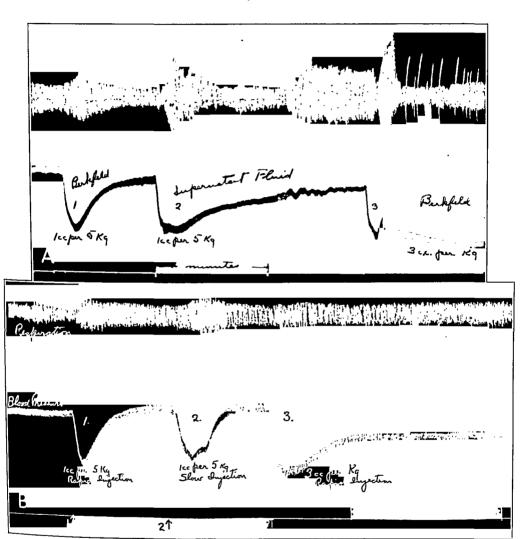
Fig. 4.—Kymograph series III, showing the toxicity of drainage material from an isolated duodenal loop. Intravenous injections were given to a dog under ether anesthesia. The spaces between the arrows represent five minute periods. *A* was obtained following the injection of bile-free drainage material from a loop so constructed as to contain pancreatic juice and duodenal secretion only; *B*, following the injection of drainage material from a duodenal loop receiving both bile and pancreatic juice.

appeared to be in good condition for three days during which time the drainage was collected into small rubber balloons for periods of several hours. This enabled

us to collect more than 200 cc. of secretion without overdistending the loop. At the end of four days the dog died. The loop was discolored but not perforated. There was no peritonitis or other grossly discernible cause of death. The toxicity of the stagnant contents was approximately the same as that of fresh specimens.

TABLE 3.—*Toxicity of Drained Pancreaticoduodenal Secretion*

Test Animal	Material Injected	Intravenous Dose*	Result
Dog 636	Drainage from duodenal loop, dog 624; supernatant fluid	3 cc.	Died in 12 hours
Dog 635	Drainage from duodenal loop, dog 624; Berkefeld filtrate	3 cc.	Died in 12 hours
Rabbit 45	Drainage from duodenal loop, dog 624; supernatant fluid	5 cc.	Died in 12 hours
Rabbit 43	Drainage from duodenal loop, dog 624; Berkefeld filtrate	5 cc.	Recovered

* Per kilogram of body weight.

TOXICITY OF OBSTRUCTED INTESTINAL CONTENT

Obstruction of any part of the small intestine produces at once a rapid accumulation of secretions which seems to be increased over the normal. Since reabsorption of fluid is never a major function of the small intestine, there ensues at once a metabolic disturbance due to loss of fluids, chlorides and other electrolytes, a phase of the problem which is now thoroughly appreciated and need not be discussed here. The present study concerns the effect of obstruction on the toxicity of the intestinal contents.

The material within the lumen of the obstructed intestine usually becomes brownish red or tarry, owing to decomposition of extravasated blood. It is foul-smelling and generally bad in gross appearance (the changes are due chiefly to bacterial putrefaction). The demonstrable toxicity of such material, however, is extremely variable. The variability is much greater than that noted in testing the normal contents. Concerning variations in toxicity observed under different conditions of obstruction, our experiments have demonstrated the following fact:

The contents of the obstructed bowel or of the isolated obstructed loop is less toxic than normal intestinal contents unless the obstructed segment receives and retains in concentrated form pancreatic duodenal secretion, in which case its toxicity may equal or exceed the normal.

Many previous investigators have recognized the fact that a high obstruction is more rapidly fatal than a low one.[7] We also find the contents of duodenal loops more toxic than that of other obstructions

7. Maury, J. W. D.: Death in Acute Intestinal Obstruction and Kindred Conditions is Due to Physiologic Disturbance: I. Has the Duodenum a Toxic Intestinal Secretion? J. A. M. A. **54**:5 (Jan. 1) 1910. Bunting, C. H., and Jones, A. P.: Intestinal Obstruction in the Rabbit, J. Exper. Med. **17**:192 (Feb.) 1913; ibid. **18**:25 (July) 1913.

and look on the pancreatic secretion as a probable explanation. The data which we outlined in the foregoing experiment and which we have verified repeatedly are further substantiated by experiments with isolated obstructed loops.

This method of study has long been employed in the investigation of intestinal obstruction. In this procedure, isolated obstructed loops of intestine are made by sectioning the bowel in two places, turning in the ends of the section thus isolated and restoring the continuity of the gastro-intestinal tract by anastomosis. The statement has been made that animals which have undergone such sectioning present the picture of an intestinal obstruction at the level of the isolated segment.[4] This is true only in part. In many instances an animal with an isolated loop of ileum will remain essentially normal for many weeks, dying only when the loop becomes gangrenous or perforated, causing generalized peritonitis. It is astonishing to note the size such a loop may attain and the quantity of foul material that may be contained within it. Yet the loop may remain normal except for the hypertrophy. In such a case the animal remains normal and recovers promptly if the loop is removed. These statements do not apply to duodenal loops. These loops rapidly become discolored and strangulated. Seldom, if ever, does an animal survive the sectioning of a duodenal loop more than sixty hours.

These sudden changes may be explained in part by the overdistention caused by the copious secretion which pours into such a loop chiefly from the pancreas. As indicated by previous experiments,[8] necrosis or gangrene of an intestinal loop may develop as a direct result of over-distention. However, the extremely rapid necrosis in these duodenal loops suggests the intensification of this process by another factor, namely, the autodigestion of the devitalized tissue by activated pancreatic juice. The gross and microscopic indications of acute hemorrhagic pancreatitis which we have observed furnish additional evidence that this process may be an important factor in the early death which occurs under these conditions. As shown in the protocol of dog 624, however, an animal with a pancreaticoduodenal loop dies even if the loop is drained, an observation pointing to the importance of metabolic disturbances as a factor in death from high obstruction.[9]

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8. Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Effects of Gaseous Distention on Obstructed Bowel; Incarceration of Intestine by Gas Traps, Arch. Surg. **14**:1215 (June) 1927.

9. Elman, R., and Hartman, A. F.: Experimental Obstruction of the Terminal Duodenum and Ileum: The Importance of Blood Chemical Changes in Causing Death, Surg., Gynec. & Obst. **53**:307 (Sept.) 1931. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: III. Simple Obstruction: A Study of the Cause of Death in Mechanical Obstruction of the Upper Part of the Intestine, Arch. Surg. **16**:1242 (June) 1928.
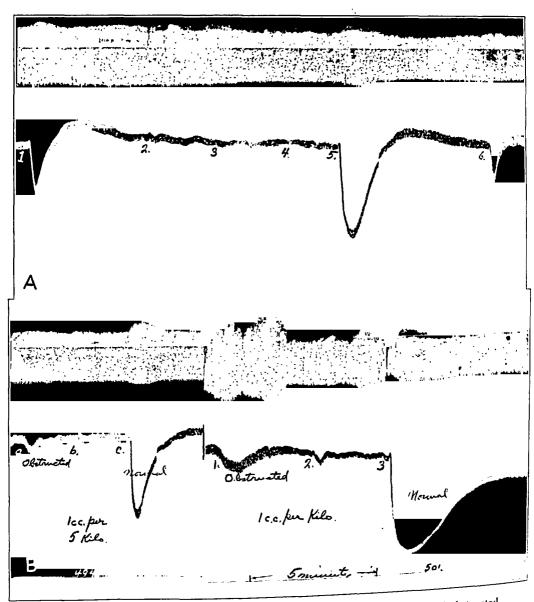
Fig. 5.—Kymograph series IV, showing the effects of the contents of obstructed intestine as compared with normal contents. Intravenous injections were given to a dog under ether anesthesia. *A* shows the results of the injection of a Berkefeld filtrate of the following material: *1.* Normal contents, dog 473, 1 cc. for each 5 Kg. *2.* contents of obstructed loop, dog 473, 1 cc. for each 5 Kg. *3.* Contents from above site of obstruction, dog 473, 1 cc. for each 5 Kg. *4.* Contents from above site of obstruction, dog 475, 1 cc. for each 5 Kg. *5.* Normal contents, dog 475, 1 cc. for each 5 Kg. *6.* Contents of obstructed loop, dog 475, 1 cc. for each 5 Kg. *B* shows slight toxicity of the contents of the obstructed intestine as compared with the normal contents in dog 475. A Berkefeld filtrate was employed.

As previously indicated, this study must be limited chiefly to a consideration of demonstrable toxicity in the contents removed. We studied, in all, sixty-eight isolated obstructed loops made at various levels of the bowel. In all the cases, with the exception of duodenal loops, we found Berkefeld filtrates of this material to be less toxic than similar preparations of normal intestinal contents. As compared to the normal contents, the filtrates of most samples from loops have no marked properties in lowering the blood pressure. Neither do they so commonly kill when injected intravenously into dogs and rabbits. Even the supernatant fluids which naturally contain large numbers of bacteria do not consistently kill on intravenous injection. Similar

TABLE 4.—*Toxicity of Contents of Obstructed Intestine as Compared with the Normal Intestinal Contents of Dogs*

Test Animal	Material Injected	Intravenous Dose*	Result
Dog 485	Sample 1: normal intestinal contents, dog 473; centrifugated supernatant fluid	3 cc.	Violent toxic symptoms; died in 20 hours
Dog 481	Berkefeld filtrate of sample 1................	3 cc.	Toxic symptoms; recovered
Dog 486	Sample 2: contents from above site of obstruction, dog 473; supernatant fluid	3 cc.	Recovered
Dog 483	Berkefeld filtrate of sample 2................	3 cc.	Recovered
Dog 487	Sample 3: contents of isolated obstructed loop, dog 473; supernatant fluid	3 cc.	Recovered
Dog 482	Berkefeld filtrate of sample 3................	3 cc.	Recovered
Dog 497	Sample 4: normal intestinal content, dog 475; supernatant fluid	3 cc.	Died in 7 hours
Dog 496	Berkefeld filtrate of sample 4................	3 cc.	Died in 48 hours
Dog 498	Sample 5: contents from above site of obstruction, dog 475; supernatant fluid	3 cc.	Recovered
Dog 499	Berkefeld filtrate of sample 5................	3 cc.	Recovered
Dog 500	Sample 6; contents of isolated obstructed loop, dog 475; supernatant fluid	3 cc.	Died in 23 hours
Dog 495	Berkefeld filtrate of sample 6................	3 cc.	Died in 48 hours

* Per kilogram of body weight.

samples of normal contents are much more consistently toxic than those from the obstructed loops. It is true that the crude material containing the tarry sludge so commonly formed in the obstructed loop is violently toxic on intravenous injection. Such material, however, is unsuitable for intravenous tests no matter what its source is.

Wangensteen [10] has previously reported the contents of an obstructed bowel to be less toxic than the normal, and our work, with the exceptions noted, bears out his observations. We consider it unnecessary to present our voluminous observations in detail. The limited data contained in tables 4 and 5, in addition to the kymographic records, present typical findings.

10. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, Arch. Surg. **16**:606 (Feb.) 1928.
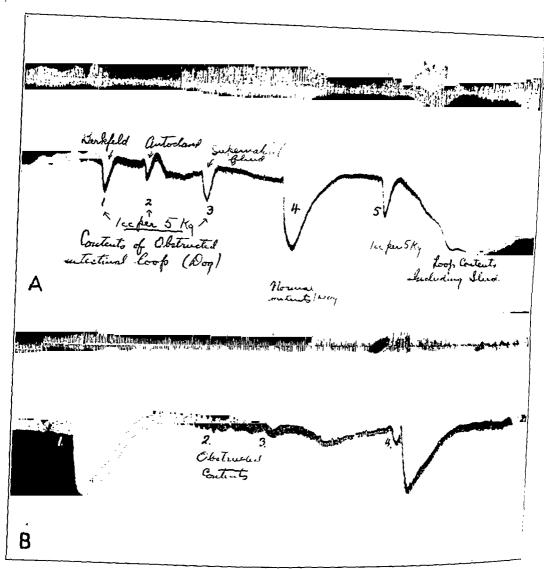
Fig. 6.—Kymograph series V. *A* shows the toxicity of the contents of obstructed intestine as compared with normal contents. The contents of dog intestine (1 cc. for each 5 Kg. of body weight) were injected intravenously into a dog under ether anesthesia. *B* shows the toxicity of the content of obstructed intestine as compared with drainage material from an enterostomy after operation. The following material (human intestine, case 1) was injected: *1.* Supernatant fluid, drainage material from enterostomy, 1 cc. for each 5 Kg. *2.* Supernatant fluid, contents of obstructed intestine, 1 cc. for each 5 Kg. *3.* Supernatant fluid, contents of obstructed intestine, 1 cc. per Kg. This injection produced no effect although the dose was increased five times. *4.* Supernatant fluid, drainage from enterostomy, 1 cc. for each 5 Kg.

In addition to the observations on dogs we have studied the contents of obstructed human intestine in sixteen cases. Most samples of this material possessed slight toxicity as compared to the drainage material which was subsequently obtained from the enterostomy above the obstruction. A few samples from obstructed bowel were found to be innocuous as portrayed in kymographic record V (fig. 6) showing the tests in case 1. In this patient after a few days the drainage material from the enterostomy acquired the toxicity typical of the normal con-

TABLE 5.—*Toxicity of Obstructed Intestinal Contents*

Test Animal	Material Injected	Intravenous Dose*	Result
Dog 569	Sample 1; supernatant fluid, contents of loop, dog 549†	3 cc.	Severe toxic symptoms; died in 4 hours
Dog 570	Berkefeld filtrate of sample 1..............	3 cc.	Mild symptoms; recovered
Dog 340	Sample 2; combined contents of several isolated obstructed loops of ileum; supernatant fluid	3 cc.	Mild symptoms; recovered
Dog 341	Berkefeld filtrate in sample 2..............	3 cc.	Mild symptoms; recovered
Rabbit 113	Supernatant fluid; sample 2..............	5 cc.	Died in convulsions
Rabbit 75	Berkefeld filtrate of sample 2..............	5 cc.	Recovered
Rabbit 38	Sample 3; contents of isolated obstructed loop of duodenum which was fatal to dog 603 in 48 hours; supernatant fluid	5 cc.	Immediate death
Rabbit 36	Berkefeld filtrate of sample 3..............	5 cc.	Toxic symptoms; recovered
	Tests on Content Above Site of Obstruction		
Dog 498	Sample 4; contents above site of obstruction in jejunum; supernatant fluid	3 cc.	Toxic symptoms; recovered
Dog 499	Berkefeld filtrate of sample 4..............	3 cc.	Mild symptoms; recovered
Rabbit 104	Sample 5; duodenal contents above site of obstruction at ligament of Treitz; supernatant fluid	5 cc.	Convulsions; died at once
Rabbit 117	Berkefeld filtrate of sample 5..............	5 cc.	Convulsions; died at once
Dog 292	Sample 6; contents above site of obstruction (ileum) in man, case 1; supernatant fluid	3 cc.	Died in 24 hours
Dog 294	Berkefeld filtrate of sample 6..............	3 cc.	Recovered
Rabbit 59	Supernatant fluid; sample 6..............	5 cc.	Died in 48 hours
Rabbit 61	Berkefeld filtrate of sample 6..............	5 cc.	Recovered

* Per kilogram of body weight.
† This was a 2 foot loop of high jejunum of dog 549 which survived for 9 days, at which time he was killed.

tents of the small bowel. In this case the enterostomy was high in the jejunum, and its drainage material would naturally contain a great amount of the combined pancreaticoduodenal secretions. Drainage from a low enterostomy usually shows less toxicity.

Proctocols—(Dogs 473 and 475).—Two dogs (473 and 475) were anesthetized with ether after twenty-four hours' starvation. In each animal the abdomen was opened; the jejunum was sectioned with the cautery about 8 inches (20 cm.) below the ligament of Treitz. The normal fluid contents of the duodenum and jejunum were collected and kept for testing. The jejunum was again sectioned about 3 feet (91 cm.) below Treitz's ligament. All the stumps were inverted, and no anastomosis was made. By this procedure we produced in each case a jejunal obstruction in addition to an isolated obstructed loop of jejunum.

Dog 473 was killed two days later, when in fair condition. The loop was intact but distended with a large amount of fluid. The contents of the loop and also the material above the site of the obstruction were tested and found much less toxic than the normal, as shown in table 4 and in kymographic record (fig. 5).

Dog 475 was explored at death, seven days after the obstruction. The loop was gangrenous and showed a small perforation, causing death from peritonitis. The contents of the loop were more toxic than in dog 473 (chemical studies showed the contents of the loop of dog 475 to contain large amounts of histamine). Neither the contents of the loop nor the material above the site of the obstruction was equal to the normal in toxicity.

GENERAL COMMENT

Many questions naturally arise from the foregoing observations. What are these toxic substances? Are they absorbed? If so, how and under what conditions? How can the reduced toxicity of the contents of the obstructed bowel as compared to that of the normal contents be explained? These are only a few, but even they cannot be answered in full at this time. By studies still in progress we hope to make further contributions, but at present we are justified in making only a few general comments.

Histamine produces effects comparable to the reaction we have described, and, as Gerard [11] reported, is present in varying but usually small amounts in practically all the samples of intestinal contents. We found, however, in our preliminary tests that samples of normal intestinal contents retain most of the toxic property after the histamine is removed. In filtrates of the contents of obstructed intestine which we tested similarly, the removal of histamine left little or no toxicity.

Concerning causes of the reduced toxicity in the obstructed intestine as compared to that in the normal bowel we have no definite explanation. In the contents of low isolated obstructed loops it is obvious that little or no normal toxicity is present when the loop is formed, and the toxicity which is acquired must be due to bacterial putrefaction (the formation of histamine and other toxins). Under other conditions in which normal toxicity must be present in the contents at the outset, the disappearance or reduction in potency may be due to destructive putrefaction. There is the possibility, for which we have no proof, that the toxic substances may be removed by absorption.

As for this phase of the problem we have seen nothing to contradict the statements we have previously made that in simple obstruction, so long as the intestinal wall remains intact, there is no absorption of toxins sufficient to cause death.[2] When, however, the wall becomes gangrenous. there is ample evidence that any of these substances may slowly pass

11. Gerard. R. W.: The Lethal Agent in Acute Intestinal Obstruction. J. A. M. A. **79**:1581 (Nov. 4) 1922.

through transperitoneally, just as they are dialyzed through a dead membrane. As for the possibility that absorption may occur into blood or lymph with lesser degrees of injury from overdistention or strangulation, no satisfactory proof has been produced experimentally. However, the mere absence of such convincing evidence is not necessarily a proof of the negative. Even though toxins were absorbed, they might be destroyed or taken up by the tissues, or otherwise rendered undetectable. In fact, the transient effect on the blood pressure following intravenous injection is evidence that this must be to a large extent true.

Though these questions remain unanswered, the observations we have reported are somewhat enlightening. It appears that little significance need be attached to the finding of toxins in the obstructed bowel, when even more potent toxins are normally present within the lumen. Furthermore the statements to the effect that intravenous injection of these toxins leads to resecretion [12] into the upper part of the intestine are open to question on the same basis. We have investigated these claims and, as previously stated, we find the normal pancreaticoduodenal secretion more toxic than any material we have tested. Aside from this material we find no toxin secreted into the upper part of the intestine following the intravenous administration of contents of an obstructed bowel. In general, we find no basis for the assumption that intestinal obstruction leads to the formation of a specific toxin. We find toxic substances normally present within the lumen of the bowel, their chief source being the pancreaticoduodenal secretion. In high obstruction artificially produced in the dog we find definite evidence that necrosis and autolysis of tissue by activated pancreatic juice is the most important factor in the rapid death which occurs. We are not at present prepared to discuss this subject in full, and autopsy studies have not revealed pancreatic necrosis in fatal cases of intestinal obstruction in man.

It is quite apparent that many factors must be involved in the problem of intestinal obstruction, and nothing is gained by attempting to explain the mechanism of death on the basis of one single factor. Much valuable information has been accumulated in the past few years, and, on the whole, we have at least as many scientific data on the subject of acute intestinal obstruction as are available for any other problem in medicine. We are still attempting to solve the question, "Are toxins absorbed; if so, how and under what conditions?" But it seems likely that its solution is chiefly of academic interest. From a practical standpoint the chief cause of death in acute intestinal obstruction is the delay which so commonly preceeds the proper treatment.

12. Sweet, J. E.: Intestinal Obstruction, Experimental Research, Internat. Clin. **1**:72, 1920.

CONCLUSIONS

1. The normal contents of the bowel in dogs and in human subjects is always toxic when injected intravenously into animals.

2. Admitting the presence of many substances which may contribute to this toxic property, the chief source of the toxin appears to be the pancreaticoduodenal secretion.

3. The contents of the obstructed bowel or of an isolated obstructed loop is less toxic than the normal intestinal contents, unless the obstructed segment receives and retains in concentrated form the pancreaticoduodenal secretions, in which case its toxicity may equal or exceed that of the normal contents.

4. Methods of testing the material, the significance of the results obtained, the question of toxemia and other causes of death have been presented.

DIATHERMY AND REGENERATION OF BONE

E. DAVID WEINBERG, M.D.

Instructor in Orthopedic Surgery, Johns Hopkins University

AND

GRANT E. WARD, M.D.

Instructor in Surgery, Johns Hopkins University

BALTIMORE

The value of heat as a potent agent in treating disease has long been recognized. Therapeutic heat is given in various ways; its penetration formerly depended on radiation from some hot, external object. With the advent of diathermy [1] a new form of application of heat was given to the medical profession. The value of diathermy theorectically depends on the development of heat within the tissues by the passage of a high frequency electric current through them. Whether there is some as yet unknown electromagnetic effect remains for further study, and does not fall within the scope of this paper. Because the heat is generated within the tissues, instead of coming from an external object, it should be more penetrating and, therefore, more effective than any other previous thermotherapy. Such claims are advanced in the literature, although since the time of d'Arsonval insufficient scientific investigation has been made to prove the actual penetrating qualities and mode of production of this heat and its effectiveness in the deeper tissues. In recent years much has been accomplished toward solving these problems, so that thermotherapy may now be more rational and be placed on a firmer scientific basis.

Much has been written concerning the value of diathermy in the treatment of fractures, especially in hastening delayed union. Of course, the disease causing the delay in union is an important consideration, but we believed that this problem should be studied first under as nearly normal conditions as possible. When we began these studies, we were skeptical as to the rise in deep temperature, particularly within osseous tissue—which is a poor conductor of electricity—and still more doubtful as to the value of diathermy in delayed union. A large amount of skepticism has been erased, as the microscope demonstrated an increase in formation of new bone when diathermy was used.

1. d'Arsonval, A.: Compt. rend. Soc. de biol. **43**:283, 1891.
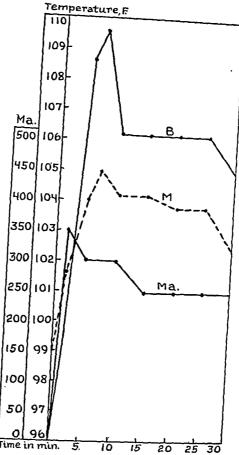
Fig. 2.—Graph showing changes in temperature in bone (B) and muscle (M), with variations in milliamperage (Ma).
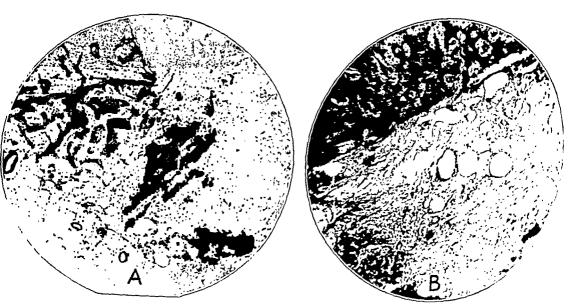
Fig. 3.—A, photomicrograph of the left leg after diathermy for one week, showing marked periosteal and endosteal formation of new bone. Note the highly vascularized marrow and numerous osteoblasts lining the newly formed trabeculae of bone. B, photomicrograph of the right leg after control observation for one week. Slight periosteal formation of new bone is seen.

to the treatment. Shortly after turning on of the current there was a free flow of blood, but as soon as the heat was discontinued and the leg allowed to cool a little, the bleeding stopped. This occurred with such regularity that we were forced to conclude that the heat or perhaps some other electromagnetic effect of the diathermy dilated the blood vessels, allowing free escape of blood into the wound. We assumed then that any beneficial effects, such as increased formation of new bone following diathermy, would probably be due to the increased circulation.

Diathermy electrodes, sterilized by boiling, were on one occasion applied while hot, water from the sterilizer being retained in the rubber 'sponges. As soon as these hot electrodes touched the leg a rapid rise in temperature occurred, in both the muscle and the bone, demonstrating that with such a small part of the body as the dog's forelegs, external heat will also raise the temperature of the bone. This seems to indicate that in these animals, at least, therapeutic effects can be obtained by the external application of hot objects. In clinical use, however, particularly in dealing with the large limbs of human beings, diathermy heat is more readily applied and probably penetrates more deeply. To prove this and to determine whether this type of external heat will stimulate formation of new bone, along with increasing temperature, require further investigation.

Considerable time was required and several animals were killed before our technic was sufficiently standardized for application to a well controlled series of animals. Nine dogs were used in the final group. Sloughing of the skin developed in one of these, so that it had to be eliminated. Our results, therefore, are based on eight successfully treated and controlled animals. During the first treatment, readings of the temperatures of the bones and muscles and the milliamperage were taken at the beginning of the experiment and every five minutes during the time that the current flowed. These readings were tabulated to form curves representing the rise and fall of the temperatures, with the rise and fall of the milliamperage as abscissas and the time as ordinates.

Figure 8 is a composite chart of the dogs in our series. The mean variations in milliamperage and the rises in temperature in the bones and muscles are all represented. It will be noted that, on the whole, the rise in temperature of the muscles and that of the bones are nearly parallel. The temperature of the muscles rises a little faster at first, to be overtaken later by the temperature of the bones, which, near the end of the experiment, again falls. These variations are hard to explain and for our purposes were not further studied. The main object of the investigation was to secure an actual rise in temperature in the bone, which we could reproduce at will by repeating the exact application of current determined at the time of the operation, which gave
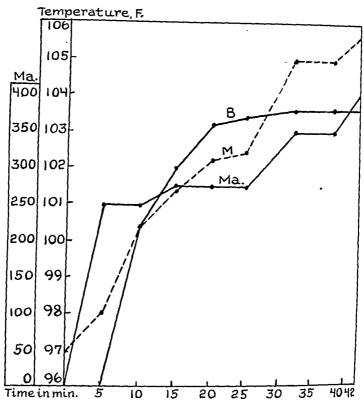
Fig. 4.—Graph showing changes in temperature in bone and muscle, with variations in milliamperage.
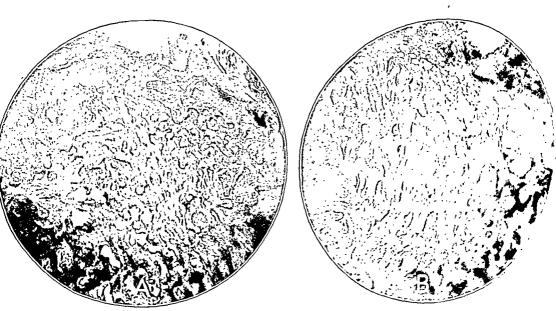
Fig. 5.—*A*, photomicrograph of the left leg after diathermy for two weeks. Note the rich periosteal and endosteal callus with a highly vascularized marrow which completely fills the region. *B*, photomicrograph of the right leg after control observations for two weeks. This section, from the region in which an osteotomy was done, is partially filled with endosteal callus. Note the almost complete absence of perisoteal callus.
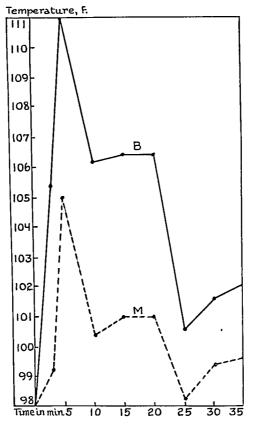
Fig. 6.—Graph showing changes of temperature in bone and muscle (skin).
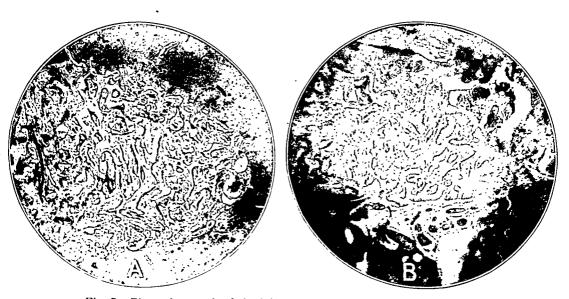
Fig. 7.—Photomicrograph of the left leg after diathermy for four weeks. The defect is almost completely filled by compact bone, rich in haversian canals. *B*, photomicrograph of the right leg after control observations for four weeks. The region in which osteotomy was done is filled with a newly formed lamellar type of bone arising mainly from the endosteum.

the rise in temperature in the bone above the normal and yet within physiologic limits. That this was obtained and gave definite beneficial results is verified by the results of the postmortem examinations.

Microscopic Changes.—One Week (figs. 2 and 3): In the treated leg the hole was filled with vascularized connective tissue, a few degenerated red blood cells and a small amount of bone dust. An attempt at formation of new bone was evident, arising from the cut edges of the endosteum. The endosteum in the neighborhood of the hole showed a
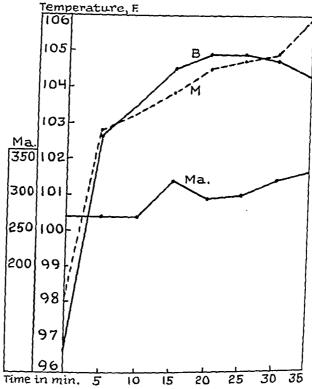
Fig. 8.—A composite chart of seven experiments showing average changes in the temperature of the bones and muscles, with variations in milliamperage and time, as determined at the operation. At subsequent treatments the same milliamperage was maintained, with the expected rise in temperatures of the bones and muscles.

marked proliferation of osteoid tissue extending down into the marrow cavity and the marrow cavity near the hole was filled with young fibrous connective tissue, which was highly vascularized.

In the control leg the hole was filled with a partially organized blood clot, fibrous connective tissue, degenerated red blood cells and bone dust, undergoing partial absorption. The cut edges of the endosteum were lined by fragmented bone with the bone cells missing. The cut edges of the cortical bone were lined by bone dust and fibrous connective tissue and occasionally by osteoblasts.

Two Weeks (figs. 4 and 5): The treated leg showed marked formation of new bone arising from the periosteum, the endosteum and the cut edges of the compacta. There was also evidence of formation of new bone in the marrow, with consequent narrowing of the medullary cavity.

In the control leg there was some periosteal new bone in the immediate neighborhood of the hole, with some osteoid tissue—not yet bone—arising from the cut edges of the endosteum. The cut edges of the compacta were lined with unabsorbed bone dust, with an occasional osteoblast. The medullary cavity was filled with blood and with bone dust partially absorbed by fibrous connective tissue.

Three Weeks: In the treated leg there was a decided advance in the periosteal and endosteal formation of new bone. The cut edges of the endosteum were lined with osteoblasts. There was a marked proliferation of bone in the medullary cavity, so that it was almost completely filled.

There is no periosteal new-bone formation, and only a slight amount of endosteal new bone in the control leg. The medullary cavity was far from being completely filled with bone. Along the site of the hole made by the drill the cavity was filled with a partially organized blood clot and some bone dust. Other portions of the marrow appeared to be normal, so that the osteogenesis was local.

Four Weeks (figs. 6 and 7): The treated leg revealed marked new periosteal bone. The hole was completely filled with a compact type of bone (not the young lamellar type) and looked like old cortical bone, except for an increase in haversian canals, which were more vascular and contained a larger number of young fibroblasts than usual.

In the control leg there was little or no periosteal new bone, and the hole was filled with a lamellar type of bone, so that it was not yet healed.

CONCLUSIONS

1. In experimental animals diathermy properly applied will raise the temperature of the bones and muscles.

2. The rise in temperature increases the local circulation.

3. Such increased physiologic activity accelerates the formation of new bone.

1208 Eutaw Place.

214 Medical Arts Building.

LIPOMA PSEUDOMYXOMATODES OF THE UPPER EXTREMITY

MAX THOREK, M.D.

Professor of Surgery, Cook County Graduate School of Medicine, Surgeon-in-Chief, American Hospital of Chicago, Attending Surgeon, Cook County Hospital

AND

PHILIP THOREK, M.D.

CHICAGO

Atypical lipomatous tumors have been described under a variety of names, such as "myxoma lipomatodes," "lipoma myxomatodes," "myxofibrolipoma" and "myxosarcolipoma," according to the structure of the tumor and the pathologist's point of view. The literature shows that most of these atypical lipomatous growths occur in the intramuscular tissue of the lower part of the body, especially in the groin and upper thigh. The term "lipoma pseudomyxomatodes" has been applied to certain of these atypical tumors, the fat cells of which they are principally composed being immature and atypical, capable of proliferating and forming a syncytium-like structure and producing a mucoid intercellular substance.

The case reported here of a tumor of this type is of interest because of the unusual location of the growth and because, possibly, the histologic observations may be a contribution to the interpretation of the myxomatous changes taking place in the structure of the tumor mass.

REPORT OF A CASE

History.—J. E., a white man, aged 57, was admitted to Cook County Hospital on Oct. 11, 1932. The patient stated that he had always been well until six or seven years before admission, when a small soft swelling was observed on the posterior aspect of the left shoulder. It was painless and without other subjective symptoms. This swelling gradually increased in size until it was difficult for the patient to put on his clothes. No other swelling was observed at any time. The history disclosed no other important disease, but the right forearm had been amputated, following an injury.

Examination.—The patient did not appear to be acutely ill; there was no loss of weight; his appetite was good; no constipation or diarrhea was complained of. The head, neck and chest were normal, except for carious teeth. The abdomen was soft and relaxed and no masses were felt.

The cardiovascular and genito-urinary systems were normal. The urine had a specific gravity of 1.018, an acid reaction, a trace of albumin and occasional granular casts and pus cells, but no sugar. The blood pressure was 164 systolic and 98 diastolic.

From the Surgical Service of Cook County Hospital.
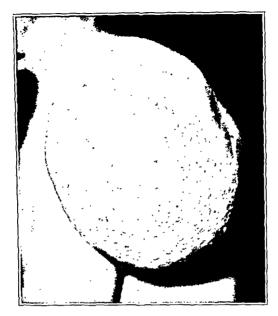
Fig. 1.—Lipoma pseudomyxomatodes; lateral aspect.

Fig. 2.—Lipoma pseudomyxomatodes; posterior view.

On the posterior aspect of the left shoulder was a soft mass larger than the patient's head. It was irregular in contour; expansible pulsation was not evident. The mass was crossed by many large, dilated veins and a large pulsating artery could be seen at the acromial border. The clinical aspects are portrayed in figures 1 and 2, which show the lateral and dorsal views of the tumor mass. Inspection and palpation of the tumor gave the impression that it was lipomatous.

Operation.—The tumor was found to be a large multilocular cystic mass, which was easily excised. The sutures were removed on the seventh postoperative day and the patient left the hospital in good condition on the following day. The postoperative course was afebrile.

The soft gelatinous mass removed measured 22 by 20 by 10 cm. and weighed about 1½ pounds (780.4 Gm.).
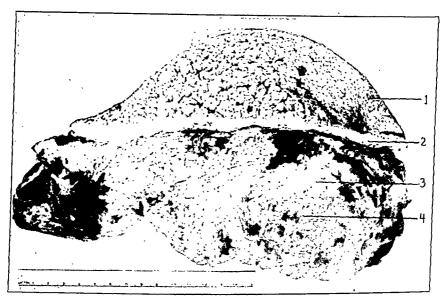
Fig. 3.—The excised tumor, showing (*1*) skin, (*2*) subcutaneous tissue, (*3*) lobules of intact fat tissue and (*4*) extensive areas of myxomatous degeneration.

Pathologic Examination.—The pathologist's report follows: "Macroscopic: The specimen is a large tumor mass 22 by 20 by 10 cm., which is covered on one side by a piece of skin and subcutaneous tissue measuring 12 by 20 cm. The tumor is moderately soft and fairly well circumscribed, although it has no definite capsule. The cut surface has a variegated appearance. Some areas are bright yellow, but most of the surface is light gray and mucoid in appearance, with stringy mucoid material exuding from it. There is a small amount of hemorrhagic mottling (fig. 3).

"Microscopic: Part of the section is composed of large fat cells with a delicate intercellular stroma. In many areas this stroma becomes loosened and slightly more cellular. The changes can be followed up to an extreme degree of interstitial loosening of the stroma, so that the tissue seems to be composed of an edematous fibrillar material in which the finest fibrils are individually isolated. A rich network of fibrils protrudes from each connective tissue cell. All of this tissue is embedded in a diffuse bluish-staining hyaline ground substance."

The diagnosis was lipoma pseudomyxomatodes.
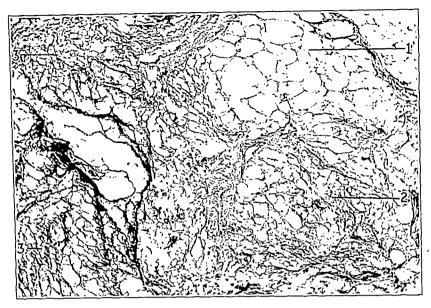
Fig. 4.—Photomicrograph of lipoma pseudomyxomatodes, showing (*1*) lipomatous tissue, (*2*) early myxomatous transformation and (*3*) advanced myxomatous metamorphosis; reduced from × 120.
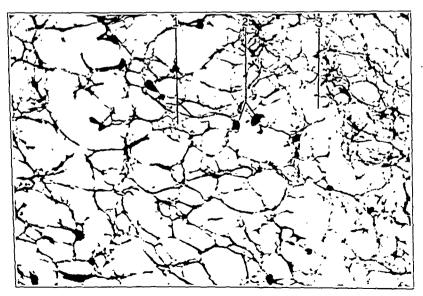
Fig. 5.—High power magnification (× 540) of myxomatous area, showing extensive fibrillar loosening of the myxoma-like cells, embedded in a mucoid ground substance: (*1*) extensive loosening and separation of the fibrils of the connective tissue: (*2*) nuclei of myxoma-like cells, and (*3*) mucoid ground substance.

COMMENT

Atypical lipomatous tumors, composed of mucinous and fat tissue, are not very rare. They may be benign or may have undergone malignant degeneration. In 1916 Robertson[1] collected reports of fifty-one cases from the literature. In seventeen of these cases the growth was situated retroperitoneally; in three it was in the mesentery and in most of the remainder it was in the leg or arm. Thirty-three per cent of the fifty-one tumors were malignant, and since 1916 many other malignant lipomatous tumors have been recorded.

Cases of atypical lipomatous tumor situated in the upper extremity are rather infrequent. Since Robertson's report I can find in the general literature record of only one case and this case was similar to ours. Rose,[2] a few years ago, reported a case of pedunculate lipoma situated on the inner side of the upper part of the arm of a woman (age not stated). The growth, which weighed 8½ pounds (3,855 Gm.), had been in existence for twenty-five years, and seemed to be undergoing mucoid degeneration. The pedicle contained several veins and one large artery.

The question of malignant changes in lipomatous tumors has received much attention. Pure lipomatous malignant tumors, such as the true liposarcoma, occur rarely and, according to many authors, it is probable that the lipomatous tissue is really a fatty degeneration of the sarcoma. For instance, in the case reported by Jaffé[3] the tumor was a sarcoma with extensive fat deposits in the cells. He therefore diagnosed the tumor as a liposarcoma.

On the other hand, the occurrence of true fatty degeneration has been denied. Lipvendahl[4] expressed the belief that it is out of the question: that lipomatous tumors chiefly occur in those parts of the body where the amount of fat is greatest; and he suggested that globules of fat are formed within the cells, coalescing and appearing as large bodies of fat in the cytoplasm. Moreover, there is the opinion defended by Jacobson[5] and others that under certain conditions mucin can be produced by fibroblasts; that in fact the fat cell is essentially a modified fibroblast.

Myxomatous degeneration of lipomatous tumors has been reported or suggested in a number of cases and has given rise to controversy as to what it really signifies. Jaffé[3] summarized the opinions expressed

1. Robertson, H. E.: Lipoma, J. M. Research **35**:131, 1916.
2. Rose, B. T.: A Case of Pedunculated Lipoma of the Upper Arm, Brit. J. Surg. **15**:525, 1928.
3. Jaffé, R. H.: Recurrent Lipomatous Tumors of the Groin, Arch. Path. & Lab. Med. **1**:381 (March) 1926.
4. Lipvendahl, R. A.: Liposarcoma of the Mammary Gland, Surg., Gynec. & Obst. **50**:81, 1930.
5. Jacobson, V. C.: J. Cancer Research **6**:109 (April) 1921.

in the literature in reporting a case of lipoma pseudomyxomatodes. He stated that, as shown by the histologic examination in his case, the mucoid parts of the tumor were not true myxoma tissue but areas of mucoid degeneration resulting from an extensive edematous loosening of the connective tissue. Hence the name "lipoma pseudomyxomatodes." However, that this is not merely an ordinary degenerative change is evident by the presence of many centers of growth, consisting of young, immature fat cells. It is these young and immature, rapidly growing fat cells that undergo myxomatous transformation. But these fat cells are different from the cells of a true myxoma. According to Jaffé the close relationship between myxomatous and fat tissue during embryonic life explains the observation that fast-growing immature fat cells sometimes resemble mucin cells without really being transformed into them. In the present case figure 5 shows very clearly the early and advanced myxomatous transformation of lipomatous tissue.

It appears that there are some questions still to be settled in regard to the nature of atypical lipomatous tumors, especially of the class known as lipoma pseudomyxomatodes.

CHROMAFFIN CELL TUMOR CAUSING PAROXYSMAL HYPERTENSION, RELIEVED BY OPERATION

FREDERICK A. COLLER, M.D.

HENRY FIELD, JR., M.D.

AND

THOMAS M. DURANT, M.D.

ANN ARBOR, MICH.

The first satisfactory description of a chromaffin cell tumor (otherwise known as paraganglioma, perithelioma or pheochromocytoma) is credited to Berdez [1] in 1892. These tumors occur usually in the suprarenal medulla, but have been found in other locations in which there may be chromaffin tissue. This tissue is distinguished, as its name implies, by its affinity for chromates, which stain the cells brown. It has its embryonic origin in sympathetic ganglion cells which in turn are the result of migration and differentiation of cells from the neural crest. It is embryologically and functionally distinct from suprarenal cortical tissue.

Epinephrine being secreted by chromaffin cells, it is not surprising that tumors of this tissue should be associated with hypertension. In 1897 Neusser [2] described two patients—one a man of 25 years—both of whom died of cerebral hemorrhage and in whom no cause for hypertension was found other than tumors of the suprarenal bodies (carcinomatous degeneration). He definitely postulated that in these cases hypertension was caused by an increased production of the physiologically active secretion of the suprarenal bodies.

However, these tumors are rare. The early reports consisted almost solely of histologic descriptions of the tumors. Even in more recent reports the clinical descriptions have often been incomplete, the tumor having been accidentally discovered at autopsy; the reported clinical findings have not been constant, and different anatomic diagnoses have been associated with similar clinical conditions.

It seems desirable to attempt to clarify the situation and to establish a basis for clinical diagnosis if possible. If the condition is diagnosed, these cases are amenable to surgical cure because the tumors, in almost all cases, have been well encapsulated and are free from metastases.

1. Berdez: Contribution à l'étude des tumeurs des capsules surrénales, Arch. d. méd. expér. et d'anat. path. 4:414, 1892.

2. Neusser, E.: Die Erkrankungen der Nebennieren, in Nothnagel, H.: Spezielle Pathologie und Therapie, Vienna, Alfred Hölder, 1897, vol. 18, p. 71.

A number of the more recent cases which have been reported in detail have had a striking clinical picture in which the hypertension has occurred in paroxysms with a characteristic symptomatology. There have also been symptoms suggestive of the paroxysmal hypertensive syndrome in some of the other cases about which information is not as complete.

It is our purpose in this paper to report a new case of chromaffin cell tumor with paroxysmal hypertension in which resection of the tumor gave relief, and to review the cases about which there is some clinical information. The present case is the fourth one in which there has been relief by surgical intervention. In two of those with relief by operation the condition was not diagnosed as chromaffin cell tumor, but the cases seem to belong in this group for reasons which will be discussed later.

REPORT OF CASE

C. S., a boy, 16 years of age, entered the University Hospital with the chief complaint of attacks of dyspnea, sweating, headache, precordial oppression, nausea and vomiting. These attacks had occurred two or three times a week over a period of five months prior to his admission. They occurred usually at night and came on without apparent cause. An attack lasted several hours. Between attacks the patient felt well except for some dyspnea and palpitation on exertion. The history was irrelevant except for asthma in May and June every year since the age of 6 months. There had been nocturia (once or twice a night) for one and one-half years.

Physical examination revealed a fairly well developed and well nourished boy. The pupils were regular and equal and reacted normally in accommodation. Ophthalmoscopic examination showed endarteritis and periarteritis with fresh and old hemorrhages. There was a considerable degree of oral sepsis. The apical impulse of the heart was palpable 10 cm. to the left of the midsternal line in the fifth intercostal space. The heart sounds were regular and of good quality. There was a loud, blowing systolic murmur, with maximum intensity in the second intercostal space just to the left of the sternum, also heard over the entire precordium. The blood pressure was 125 systolic and 105 diastolic. Examination of the lungs gave entirely negative results. Palpation of the abdomen revealed no masses, palpable organs or areas of tenderness. There was no edema of the extremities. The reflexes were normal.

The Kahn reaction of the blood was negative. Repeated specimens of urine showed an intermittent albuminuria, some specimens showing as much as 3 plus albumin. Casts in varying quantities up to 10 per low power field were found from time to time. Hemoglobin determinations and the red cell, white cell and differential counts were normal. Elimination of phenolsulphonphthalein was 52 per cent in two hours. A concentration test disclosed an ability to concentrate to a specific gravity of 1.023. An electrocardiogram showed a sinus tachycardia and inversion of the T waves in leads I and II. Roentgenograms of the chest demonstrated peritruncal infiltration extending into both apexes. An orthodiagram showed the size of the heart to be within the limits of normal variation. Ordinary roentgenograms of the kidneys and pyelograms showed no definite abnormality.

Following the patient's admission it was noticed that coincident with the attacks there was a marked fluctuation of blood pressure. This is well illustrated by figure 1, in which the blood pressures determined every few minutes over a two-hour period are recorded. Figure 2 shows the routine daily blood pressure determinations. Later in the course of the patient's illness the rapid fluctuations were no longer observed, the blood pressure rising to a level between 280 and 340 systolic and remaining at this level, with minor fluctuations, for several hours before dropping again to within normal limits. During the attacks the patient perspired profusely. The extremities were cold and clammy. The lips appeared slightly cyanotic. The patient complained of headache, precordial oppression or pain, dyspnea and occasionally epigastric pain associated with nausea and vomiting. Examination of the heart and lungs during the attack revealed no changes
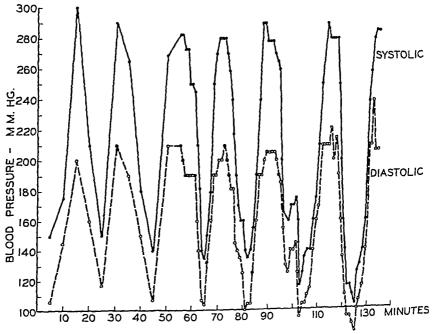
Fig. 1.—Marked fluctuations of the blood pressure during a paroxysm of hypertension.

other than the slowing of the heart rate, which was a constant accompaniment of the hypertensive phases. There was no elevation of blood sugar or nonprotein nitrogen during the attacks. The effect of various drugs on the paroxysms of hypertension was noted, and the only striking effect was that produced by the inhalation of amyl nitrite, which caused a sudden drop in pressure of from 100 to 150 mm. with an associated severe sensation of dizziness. The effect of epinephrine given in the intervals between the attacks was also noted; the patient showed marked hyposensitiveness to epinephrine as compared with the effects noted by Jensen[3] in normal and hypertensive persons given injections of the drug.
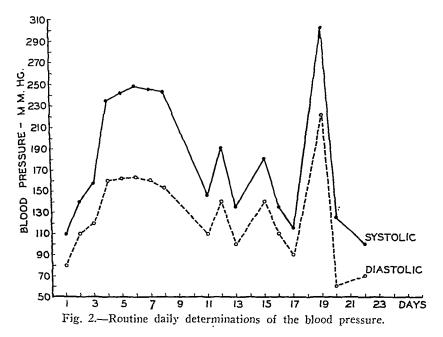
As time went on the patient's attacks became more severe and more frequent, occurring almost daily. During one attack acute pulmonary edema developed, with

3. Jensen, J.: Adrenalin Test in Hypertension, Am. Heart J. **5:**763 (Aug.) 1930.

the expectoration of considerable quantities of frothy, blood-stained sputum. It was decided at this time that exploratory laparotomy, performed in the hope of discovering a suprarenal tumor, should not longer be delayed.

The anesthetic chosen was nitrogen monoxide and oxygen. However, on administration of this anesthetic, the patient suddenly collapsed, becoming markedly cyanotic and pulseless. Recovery followed the administration of oxygen.

Two days later the patient was again prepared for operation, and on this occasion was given ether anesthesia. The condition remained satisfactory during the induction, although after the operation began, the blood pressure rose from 150 systolic and 120 diastolic to 300 systolic and 140 diastolic in an hour's time. A midline incision 3 inches (7.6 cm.) long was made just above the umbilicus. The peritoneum was opened. Exploration revealed the left kidney to be essentially normal in outline, although the upper pole seemed somewhat firmer than usual.

Fig. 2.—Routine daily determinations of the blood pressure.

The spleen, liver, gallbladder, stomach and duodenum were normal to palpation. On the anterior aspect of the right kidney was a firm tumor about 8 cm. in diameter, lying lateral and superior to the hepatic flexure. A transverse incision was then made from the medial incision through the entire abdominal wall back to the peritoneal gutter on the right side. The tumor, as shown in figure 3, was directly under the peritoneum and occupied the anterior aspect of the kidney, lying on it without being attached to it. Its blood supply came entirely from the surrounding peritoneum and retroperitoneal tissues and not from the kidney. The renal capsule was intact. The suspensory folds of the hepatic flexure were incised and the colon retracted downward and mesially. The peritoneum was lifted and the tumor removed with ease. The peritoneum was reconstructed and the abdominal wall sutured in layers.

Shortly following the removal of the tumor the blood pressure dropped rapidly until no pressure readings could be obtained. The patient was given dextrose solution, 5 per cent, intravenously, and a saline infusion. This resulted in a tem-

porary circulatory revival, with a blood pressure reading of 95 systolic and 60 diastolic. But within a short time again no blood pressure readings were obtainable. Following transfusion the patient's condition improved markedly, the blood pressure rising to 115 systolic and 85 diastolic. The condition of the patient then remained good, and further measures to combat shock were not found necessary.

The report of the pathologist (Dr. C. V. Weller) on the tumor was as follows: This neoplasm is made up of polyhedral cells with spherical nuclei and foam structure which are arranged in small alveolar nests in relationship to the blood

Fig. 3.—Drawing of the operative field showing the relative size and position of the tumor.

vessels. This resembles some of the tumors associated with precocious puberty. It is unlikely to have given rise to metastases at its present stage of development. Chromate fixation shows a striking affinity for the chromate salts, indicating relationship to the chromaffinic system rather than to suprarenal cortical structures.

In the six months since the operation the patient has been entirely free from attacks such as he previously suffered. He has been able to resume all the activities of a boy of his age without unusual dyspnea. During two periods of observation in the hospital frequent blood pressure determinations have almost all ranged between 120 systolic and 80 diastolic and 130 systolic and 90 diastolic. Evidence of recovery from the vascular effects of hypertension in the ocular fundi and

kidneys is of interest. Ophthalmoscopic examination shows improvement in the retinal vessels. There is no evidence of fresh hemorrhages or active inflammatory changes. The urine has been consistently free from albumin, very few red blood cells have been found, and the kidneys now show an ability to concentrate to a specific gravity of 1.036.
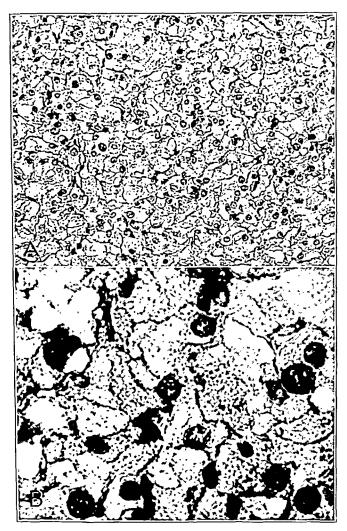
Fig. 4.—A, photomicrograph of a section of the tumor, low power magnification; B, photomicrograph of a section of the tumor, high power magnification, showing the large polyhedral cells, with cytoplasm of foam structure and chromaffin granules.

CASES FROM THE LITERATURE

We have been able to collect seventeen cases with the diagnosis of chromaffin cell tumor in which there were blood pressure determinations or in which the size of the heart was known. Another case (12) with-

out this information is listed because the symptom, rather frequent attacks of suffocation, is suggestive of paroxysms of hypertension. Two cases (19 and 20) in which other diagnoses were made are also listed because the well described paroxysmal hypertension which they showed was so similar to that of known cases of chromaffin cell tumor, proved by the chromate stain, that they seem to belong in this group. (We shall discuss later the difficulty in histologic diagnosis if chromate fixation with its characteristic brown staining of the chromaffin cells is not practiced.) These cases have been classified according to the action of the chromate stain on the tumor tissue.

A. *Positive Chromate Stain.*—CASE 1 (Herde[4]).—No clinical data were given for this patient, a woman, 62 years of age. The heart weighed 225 Gm.

CASE 2 (Herde[4]).—The patient was a man, 45 years of age. No clinical data were given. The heart, which was "much enlarged," weighed 460 Gm.

CASE 3 (Helly[5]).—A man, 43 years of age, had a condition of the heart which for a long time was regarded as "nervous," but finally was called "kidney heart." The blood pressure was described as being considerably elevated. There was intermittent glycosuria. The heart was extraordinarily hypertrophied, especially the left ventricle.

CASE 4 (Hausmann and Getzowa[6]).—A man, 53 years of age, had dyspnea and frequently coughed up bloody sputum. The blood pressure was not known. There was slight glycosuria which disappeared. Death was caused by influenzal pneumonia. The heart weighed 445 Gm., and there was hypertrophy, predominantly of the left ventricle.

CASE 5 (Biebl and Wichels[7]).—A man, 36 years old, had repeated attacks of semiconsciousness. He showed: polyuria and thirst; glycosuria, 5.5 per cent, and acetone, +. The blood pressure ranged from 208 systolic and 128 diastolic to 225 systolic and 125 diastolic. Paroxysms of hypertension were not observed. The heart weighed 450 Gm.

CASE 6 (Oberling and Jung[8]).—A woman, 28 years of age, was pregnant (at term) and complained of violent headache. There were no vasomotor or cardiac symptoms except slight edema of the legs. There were rapid fluctuations of the blood pressure, without apparent cause, from 170 systolic and 125 diastolic to 220 systolic and 155 diastolic, a condition described as paroxysmal hypertension.

4. Herde, M.: Zur Lehre der Paragangliome der Nebenniere, Arch. f. klin. Chir. **97**:937 (April 4) 1912.

5. Helly, K.: Zur Pathologie der Nebenniere, München. med. Wchnschr. **60**: 1811 (Aug. 19) 1913.

6. Hausmann, M., and Getzowa, S.: Ein Paragangliom des Zuckerkandl'schen Organs mit gleichzeitiger Herz- und Nierenhypertrophie, Schweiz. med. Wchnschr. **3**:889 (Sept. 7) and 911 (Sept. 14) 1922.

7. Biebl, M., and Wichels, P.: Physiologische und pathologisch-anatomische Betrachtungen im Anschluss an einen Fall von Paragangliom beider Nebennieren, Virchows Arch. f. path. Anat. **257**:182 (July 31) 1925.

8. Oberling, C., and Jung, G.: Paragangliome de la surrénale avec hypertension paroxystique, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:366 (March 24) 1927.

The blood pressure was once 250 systolic and 190 diastolic. Death occurred from shock following delivery. The heart weighed 450 Gm.

CASE 7 (Rabin[9])—A woman, 45 years of age, for ten years had had palpitation and dyspnea on slight exertion and tremor of the hands. The range of blood pressure in several determinations was 177 systolic and 122 diastolic to 226 systolic and 108 diastolic. The heart weighed 515 Gm., and all the chambers were hypertrophied and dilated.

CASE 8 (Schröder[10]).—A woman, 42 years old, for five years had suffered from sweats and attacks of faintness. For one and a half years she had had diabetes, which was considered to be refractory to insulin. There was no acetonuria. The blood pressure was 220 systolic and 140 diastolic. No paroxysms were observed. Autopsy revealed left ventricular hypertrophy.

CASE 9 (Pincoffs and Shipley[11]).—A woman, 26 years of age, had attacks of constriction over the heart, palpitation, dyspnea, nausea, vomiting, headache and tremor associated with paroxysms of hypertension in which the systolic rate advanced to 260 mm. of mercury. Between attacks the blood pressure was normal (120 systolic and 90 diastolic). Surgical removal of the tumor brought relief of the symptoms.

CASE 10 (Barker[12]).—A man, 46 years of age, showed weakness and mental disturbance and had had recurring convulsions for three months. The blood pressure was 200 systolic and 114 diastolic. Paroxysms of hypertension were not observed. Physical examination revealed the heart to be enlarged.

B. *Negative Chromate Stain.*—CASE 11 (Orth[13]).—The symptoms were not reported. The blood pressure was from 180 systolic and 115 diastolic to 230 systolic and 140 diastolic. Paroxysms were not observed. The heart showed marked hypertrophy and dilatation, especially of the left ventricle. The presence of epinephrine in extract of the tumor was shown by a test on a frog's eye.

CASE 12 (Masson and Martin[14]).—A woman, 45 years of age, suffered from emaciation, pain in the right side of the abdomen and frequent attacks of suffoca-

9. Rabin, C. B.: Chromaffin Cell Tumor of the Suprarenal Medulla (Pheochromocytoma), Arch. Path. **7:**228 (Feb.) 1929.

10. Schröder, K.: Eine doppelseitige chromaffine Nebennierengeschwulst mit Hypertonie, Virchows Arch. f. path. Anat. **268:**291 (June 20) 1928.

11. Pincoffs, M. C.: A Case of Paroxysmal Hypertension with Suprarenal Tumor, Tr. A. Am. Physicians **44:**295, 1929. Shipley, A. M.: Paroxysmal Hypertension Associated with Tumor of the Suprarenal, Ann. Surg. **90:**742 (Oct.) 1929.

12. Barker, L. F.: Cystic Tumor of the Medulla of the Suprarenal Gland (Paraganglioma), Associated with Early and Persistent Arterial Hypertension, with Arterial Thickening, and with Multiple Hemorrhages within the Central Nervous System, Causing Epileptiform Convulsions, Paralyses, and a Psychopathic State, M. Clin. North America **14:**265 (July) 1930.

13. Orth, J.: Ueber eine Geschwulst des Nebennierenmarks nebst Bemerkungen über die Nomenklatur der Geschwülste, Sitzungsb. d. Preuss. Akad. d. Wissensch. **1:**34, 1914.

14. Masson, P., and Martin, J.: Paragangliome surrénal. Etude d'un cas humain de tumeurs malignes de la médullo-surrénale, Bull. Assoc. franç. p. l'étude du cancer **12:**135, 1923.

tion. The blood pressure is not known, but the attacks suggest paroxysms of hypertension. The tumor was a surgical specimen. No autopsy was allowed.

CASE 13 (Zeckwer [15]).—A woman, 56 years of age, had right hemiparesis, with acute softening. The blood pressure is not known. The heart was not said to be enlarged on physical examination or at autopsy.

CASE 14 (Handschin [16]).—A man, 45 years of age, had a blood pressure of 140 systolic. Clinical symptoms of hypertension were not described. Death was caused by bronchopneumonia, following extirpation of a carcinoma of the stomach. The heart was not included in the examination at autopsy.

CASE 15 (Wichels and Biebl [17]).—A man, 33 years of age, for five years had had headaches and attacks of unconsciousness with biting of the tongue. The blood pressure was 225 systolic and 130 diastolic. Paroxysms were not noted. Death occurred from bronchopneumonia. The heart weighed 450 Gm., and the left ventricle was hypertrophied.

C. *Chromate Stain Not Done.*—CASE 16 (Labbé, Tinel and Doumer [18]).—A woman, 28 years of age, for several months had had attacks of epigastric constriction, vomiting, pallor and sweating, with paroxysms of hypertension in which the blood pressure rose to 280 systolic and 190 diastolic. She had two attacks of pulmonary edema. The blood pressure was extremely irregular; it was usually moderately elevated, although once it fell as low as 120 systolic and 80 diastolic. Death occurred with pulmonary edema. The heart weighed 340 Gm.

CASE 17.—(Labbé, Azérad and Violle [19]).—A man, 29 years of age, had paroxysms of hypertension with tachycardia, violent palpitation, pallor and sweating. The blood pressure was ordinarily around 160 systolic and 100 diastolic, but it rose to 300 or more during the paroxysms and remained there for an average of one hour. The heart weighed 350 Gm., and examination showed dilatation and hypertrophy of the left ventricle.

CASE 18 (Bergstrand [20]).—A woman, 50 years of age, died of influenzal pneumonia. The previous symptoms and blood pressure were not known. The heart weighed 500 Gm.

D. *Cases with Paroxysmal Hypertension; Tumor not Diagnosed as Chromaffin Cell Tumor; Chromate Stain Not Done.*—CASE 19 (C. H. Mayo [21]).—A woman, 30 years of age, had attacks of dyspnea, palpitation, tachycardia, tightness in the

15. Zeckwer, I. T.: Chromaffin Cell Tumor of the Adrenal Medulla (Paraganglioma), Boston M. & S. J. **193**:254 (Aug. 6) 1925.

16. Handschin, E.: Zur Kenntnis der Zuckerkandl'schen Organe, Beitr. z. path. Anat. u. z. allg. Path. **79**:728 (April 16) 1928.

17. Wichels, P., and Biebl, M.: Zur Diagnose der Paragangliome der Nebennieren, München. med. Wchnschr. **75**:656 (April 13) 1928.

18. Labbé, M.; Tinel, J., and Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale, Bull. et mém. Soc. méd. d. hôp. de Paris **46**:982 (June 29) 1922.

19. Labbé, M.; Azérad, E., and Violle, P. L.: Adénome médullaire surrénal et hypertension paroxystique, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:953 (July 8) 1929.

20. Bergstrand, H.: Suprarenal Tumor with Hypertrophy of the Heart, Hygiea **82**:321 (May 31) 1920.

21. Mayo, C. H.: Paroxysmal Hypertension with Tumor of Retroperitoneal Nerve, J. A. M. A. **89**:1047 (Sept. 24) 1927.

chest, headache and vomiting, with a rise of blood pressure from 130 systolic and 82 diastolic to 300+ systolic and 180 diastolic, pallor, sweating, frothy, bloody sputum and signs of pulmonary edema. A tumor was removed surgically, which brought relief from the attacks. Pathologic examination revealed the tumor to be a malignant blastoma.

CASE 20 (Porter and Porter [22]).—A man, 39 years of age, had attacks in which he felt "terrible"; he experienced an unpleasant sensation in the epigastrium, and his color was ashen. The systolic blood pressure would rise from 110 to 200 or more, with a slow (about 55), forcible heart beat. Surgical removal of the tumor brought relief of the symptoms. Pathologic examination revealed a suprarenal adenocarcinoma and suprarenal hypernephroma.

COMMENT

Of the ten cases yielding a positive chromate stain, nine showed evidence of hypertension. In six cases (5, 6, 7, 8, 9 and 10) there were recorded systolic blood pressures of 200 mm. of mercury or over. In another (case 3) a "considerable elevation" of the blood pressure was described, and at autopsy there was "extraordinarily marked hypertrophy" of the heart, especially of the left ventricle. In two other cases (2 and 4) with unrecorded blood pressure, the weights of the hearts were 460 and 445 Gm., respectively. In one (case 1) the symptomatology and blood pressure are not known, but the heart weighed only 225 Gm.

Of three cases in which the chromate fixation was not done, the two reported by Labbé and his co-workers (16 and 17) showed characteristic paroxysms of hypertension. The hearts were moderately hypertrophied, weighing 340 and 350 Gm., respectively. In the third case (18) the blood pressure was not known, but the heart weighed 500 Gm.

There were five cases in which a diagnosis of chromaffin cell tumor was made despite a negative chromate stain. In some the failure of the stain was explained by delay in obtaining and fixing the specimen (in our case the chromate stain was well marked in tissue which had stood unfixed, at room temperature, for twenty-four hours). In two of these five cases (11 and 15) hypertensions of 230 systolic and 140 diastolic and 225 systolic and 130 diastolic, respectively, were recorded. In the third (case 12) there is no information regarding blood pressure or the size of the heart, but the attacks of suffocation from which the patient suffered are suggestive of paroxysmal hypertension. In two cases (13 and 14) there is no evidence of hypertension or cardiac hypertrophy in the reported findings.

Therefore, in all except three of twenty cases, there was either known hypertension or indirect evidence of it. In two of the three cases

22. Porter, M. F., and Porter, M. F., Jr.: Report of a Case of Paroxysmal Hypertension Cured by the Removal of an Adrenal Tumor, Surg., Gynec. & Obst. 50:160 (Jan.) 1930.

without evidence of hypertension, the chromate stain was negative. We suggest that this may have been because of insufficient differentiation of the cells, and that for the same reason the cells may not have attained their function of secretion of epinephrine.

Hypertension alone would not serve to identify these cases clinically. But in six of the cases previously reported (6, 9, 16, 17, 19 and 20) and in our case it occurred in paroxysms with a fairly constant set of symptoms suggestive of a sudden large dosage of epinephrine. During the attack the patient complained of coldness of the extremities, precordial oppression, palpitation, dyspnea, headache, tremors and frequently nausea and vomiting. There were marked pallor and sweating. The blood pressure rose to an extremely high level, with the systolic rate frequently over 300 mm. of mercury. Both tachycardia and a slow forceful heart beat were noted. Frothy, blood-stained sputum with signs of pulmonary edema occurred a number of times. The attacks in two cases were thought to be initiated by exercise or by assuming certain positions. In the others they occurred without apparent inciting cause. The duration of an attack was from one to several hours. Between attacks the patient was usually asymptomatic, and the blood pressure was commonly normal, although in two cases it was usually observed to remain moderately elevated. This may have been due to insufficiently frequent and improperly timed determinations. Albuminuria and glycosuria occurred irregularly in some cases.

In the other cases the reported clinical data are inadequate to identify such paroxysms. In six of them some symptom was noted which is more or less suggestive of the occurrence of paroxysms. In case 4 there was frequent bloody sputum suggestive of the attacks of pulmonary edema which have been noted. The patient in case 5 had repeated attacks of semiconsciousness; the sweats and attacks of faintness in case 8 and the attacks of suffocation in case 12 are reminiscent of the symptoms described in recognized paroxysms. The patient in case 10 had recurring convulsions for three months, while in case 15 the patient had headaches and attacks of unconsciousness with biting of the tongue. The elevation of blood pressure may be so extreme in these cases that hypertensive encephalopathy would not be surprising.

It is possible that the paroxysmal nature of the hypertension was overlooked in cases in which it could have been demonstrated by more complete observations. Unless the recognition of the symptoms leads to such observations or unless frequent blood pressure determinations are made at the right times it can be readily overlooked. This is well demonstrated by figure 2 which shows daily routine determinations of blood pressure over a period of twenty-two days made in our case. A somewhat similar curve of blood pressures, showing usually a moderate

to severe hypertension is charted for case 16. It will remain for future observations to determine how common the paroxysmal hypertensive syndrome is in cases of chromaffin cell tumor. Its recognition seems to offer the only possibility of diagnosis and cure of this condition.

In addition to the two cases in which the diagnosis was not chromaffin cell tumor, but which were included in the list because of the characteristic paroxysmal hypertensive syndrome, there have been other reports of suprarenal cortical cell tumors which were associated with hypertension. Oppenheimer and Fishberg [23] collected nine such cases and added two of their own: a clinical case (with sexual precocity) and one coming to autopsy. A priori, these are difficult to understand. No pressor substance is known to be elaborated by the suprarenal cortex. One might speculate on the possibility of mechanical stimulation of the medulla by such tumors, causing an abnormal secretion of epinephrine. This, however, has not been observed in the not infrequent metastatic carcinoma of the suprarenal glands. Herde [4] in 1912 warned against the danger of a wrong diagnosis. Speaking of the chromaffin cell tumors, he said: "All these tumors have in common a rather uniform alveolar structure. The alveoli are generally separated by narrow connective tissue septums, often only by capillaries, so that pictures result which have great similarity to Gravitz' hypernephroma." Dr. C. V. Weller, in the routine pathologic examination of the specimen from our case, noted its resemblance to cortical tumor. It could readily have been diagnosed as such save for the chromate staining. In none of the cases collected by Oppenheimer and Fishberg was the use of the chromate stain reported. It would seem impossible to accept as proved such cases in which the chromate stain is not used.

The cases of cortical tumor with sexual precocity as well as hypertension are more difficult to dispose of. There were three such cases in the series collected and reported by Oppenheimer and Fishberg. However, Dr. C. V. Weller [24] said that sexual precocity has been seen not only in primary cortical cell tumor but also in metastatic neoplasms of other types invading the suprarenal glands. It would seem that judgment on these cases also must be withheld pending further observations with the chromate stain.

Paroxysmal hypertension has been reported in a few cases in which other conditions than chromaffin cell tumors have been present. Weber [25] reported a case of subacute meningococcic meningitis in which

23. Oppenheimer, B. S., and Fishberg, A. M.: The Association of Hypertension with Suprarenal Tumors, Arch. Int. Med. **34**:631 (Nov.) 1924.

24. Weller, C. V.: Personal communication to the authors.

25. Weber, C.: L'hypertension artérielle paroxystique au cours d'une méningite méningococcique subaiguë, autopsie, Arch. d. mal. du cœur **20**:598 (Sept.) 1927.

there were marked paroxysms of hypertension. Harvier and Bariéty [26] observed a case in which paroxysms of hypertension were associated with a carcinoma of the esophagus and were attributed to vagus irritation. Another similar case is that of Villaret and his co-workers [27] with a lymphosarcoma of the mediastinum. C. Aubertin [28] reported several cases of angina pectoris and of rheumatic heart disease associated with mild paroxysms of hypertension. However, these cases showed obvious pathologic processes and usually did not have associated with the paroxysms of hypertension symptoms simulating the clinical syndrome noted in the cases of chromaffin cell tumor. They should seldom be cause for confusion.

SUMMARY AND CONCLUSIONS

A new case of paroxysmal hypertension with chromaffin cell tumor which was relieved by operation has been presented and the literature reviewed.

Hypertension has been a feature in most of the reported cases of chromaffin cell tumor. In five of those previously reported, as in our case, it occurred in paroxysms with a clinically recognizable symptomatology. In others, some symptoms suggestive of such paroxysms have been noted. Subsequent observations may show the paroxysmal hypertensive syndrome to be a more constant characteristic than previous reports demonstrate.

Hypertension has also been noted in cases with a diagnosis of tumor of the suprarenal cortex. Chromaffin cell tumors may simulate cortical tumors so closely in histologic appearance that diagnoses which are not confirmed by chromate staining must be questioned until substantiated by subsequent cases in which chromate fixation is practiced.

26. Harvier, P., and Bariéty, M.: Forme laryngée du cancer de l'œsophage. Crises hypersensitives d'origine laryngée, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:176 (Feb. 6) 1925.

27. Villaret, M.; Bloch, S.; Bariéty, M., and Lappas: Crises hypertensives paroxystiques au cours d'un lymphosarcome du mediastin supérieur, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1215 (July 9) 1926.

28. Aubertin, C.: Hypertension paroxystique et œdème aigu du poumon, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1768 (Dec. 20) 1928; L'hypertension paroxystique dans l'angine de poitrine, J. méd. franç. **16**:49 (Feb.) 1927.

TUBERCULOSIS OF THE APPENDIX

HARRY KOSTER, M.D.

AND

LOUIS P. KASMAN, M.D.

BROOKLYN

In the four and one-half year period between July 1, 1928, and Dec. 31, 1932, 3,271 appendectomies were performed at the Koster Clinic; 4 appendixes showed tuberculosis. Tuberculosis of the appendix is one of the more rare manifestations of infection with the Koch bacillus in the human body. Corbin,[1] in 1837, was the first to observe such a case. In 1838, Hallowel [2] reported a death from peritonitis due to perforation of a tuberculous appendix. Following these observations a number of reports on tuberculosis of the appendix, cecum or both appeared at intervals. Koch's discovery of the tubercle bacillus, in 1882, greatly increased the impetus to the study of tuberculosis generally, and subsequently observations on this subject were reported more frequently. However, it was not until 1909, when Muller [3] published his excellent monograph on tuberculosis of the appendix, that any definitely collective statistical study was made. He collected 66 instances. In 1 case the patient died as a direct result of the operation, while in others patients died within a few months following the operation. In fact, in only 8 cases were the patients reported cured. In 1917, Scott [4] was able to find but 44 articles on the subject, 9 of which had been contributed by physicians of the United States. Since 1917, 39 articles have been written on tuberculosis of the appendix or on tuberculosis of both the appendix and the cecum or adnexa.

The late John B. Deaver considered tuberculosis of the appendix a very rare disease, while Lockwood of England and the late John B. Murphy believed that 2 per cent of all diseased appendixes are tuberculous. They also believed that if enlarged mesenteric glands are found the infection with the Koch bacillus is primary in the appendix. The frequency of tuberculosis of the appendix found at operation is given in table 1.

The frequency of tuberculosis of the appendix found at necropsy, according to Muller,[3] is given in table 2.

From the Koster Clinic, Crown Heights Hospital.

1. Corbin, M.: Gaz. méd., Paris 5:639, 1837.

2. Hallowel, E.: Am. J. M. Sc. 22:127, 1838.

3. Muller, G. P.: Univ. Pennsylvania Bull. 22:48, 1909-1910.

4. Scott, J. R.: Ann. Surg. 66:648, 1917.

According to Noehren and Mueller,[5] of 515 appendixes which came under observation in the State Institute for the Study of Malignant Disease in Buffalo, 23, or 4.4 per cent, were tuberculous.

Muller[3] stated that the disease is more common in males than in females, the ratio being 3:2. In our series of 4 cases 2 of the patients were males, and 2 were females. Most of the cases reported in the literature occurred in young adults. The lymphoid tissue in the appendix of the young adult is more abundant and the mucous membrane more delicate. Heller,[6] in a series of autopsies, found intestinal tuberculosis in 12 per cent of the adults and 26 per cent of the children. Hueppe[6]

TABLE 1.—*Frequency of Tuberculosis of the Appendix Found at Operation*

Surgeons or Institution	Year	Number of Operations	Number of Tuberculous Appendixes	Percentage
Fitz	1886	257	8	3.0
Robson	1902	300	5	1.7
Letulle	1903	300	2	0.7
Mayo	1905	1,888	29	1.5
Surgical Laboratory, University of Pennsylvania	1909	310	6	2.0
Deaver	1902-1913	7,610	16	0.2
Allen	1909	89	2	2.8
Montreal General Hospital	1909	12,003	71	0.5
Mayo	1914	1,229	3	0.1
Scott	1917	179	1	0.5
University of Minnesota Hospital	1916-1919	210	2	0.9
Free Hospital for Women, Brookline, Mass.	1902-1932	7,865	9	0.1
Koster Clinic	1928-1932	3,271	4	0.1

TABLE 2.—*Frequency of Tuberculosis of the Appendix Found at Necropsy*

Pathologist or Institution	Number of Autopsies	Number of Tuberculous Appendixes	Percentage
Fenwick and Dodwell	2,000	17	0.8*
Leseur	500	144	22.0
Kelly	3,770	44	1.2
White	56	33	59.0

* Primary tuberculosis of the appendix.

stated that the number of cases of primary intestinal tuberculosis may be reckoned as between 25 and 35 per cent of all cases of tuberculosis in children which end in death. While Fenwick and Dodwell[7] found the ileocecal region involved in 85 per cent of their autopsies on 2,000 patients with phthisis, in only 9.6 per cent was it the sole seat of the disease.

Eisendrath,[8] in 1908, reported 51 instances of tuberculosis of the appendix which he had collected from the literature and added 7 of his

5. Noehren, A. H., and Mueller, T.: Surg., Gynec. & Obst. **34**:215, 1922.

6. Quoted by Ravenel, M. P.: Proc. Path. Soc. Philadelphia **10**:73, 1907.

7. Fenwick, W. S., and Dodwell, P. R.: Lancet **2**:133, 1892.

8. Eisendrath, D. N.: The Acute Forms of Abdominal Tuberculosis, J. A. M. A. **52**:291 (Jan. 23) 1909.

own. In 1909, Muller [3] reviewed the literature and found 60 cases reported; he added 6 others that came under his observation. Scott,[4] in 1917, reported 68 cases recorded in the literature and added 1 of his own, bringing the total number of cases to 69, but he did not mention Porter's [9] case, reported in 1913, and Wilkins' [10] 2 authentic cases, reported in 1917, which we include in our review. Since then there have been no collected statistics on tuberculosis of the appendix. We have reviewed the literature and have collected all the authentic instances of tuberculosis of the appendix from 1917 to the present. We have not included any case clinically diagnosed as tuberculosis of the appendix in which an appendectomy was not performed and the appendix examined histologically. Cases of miliary tuberculosis with generalized involvement of all the organs, including the appendix, are not included.

REPORT OF CASES

The cases reported were as follows:

Porter (1913).[9]—A woman, aged 28, complained of pain in the right lower quadrant of the abdomen. Examination revealed pulmonary tuberculosis and a tender mass in the right lower quadrant of the abdomen. Laparotomy showed a mass made up of the ileum, cecum and adherent omentum. Resection of the terminal part of the ileum, of the cecum and a part of the ascending colon and ileocolic anastomosis were performed. The pathologic report was: ulcerative ileocecal tuberculosis, with involvement of the appendix. The patient was discharged from the hospital, but died five months later of bronchopneumonia.

Wilkins (1917)[10].—CASE 1.—A man, aged 26, complained of recurrent attacks of abdominal pain. Examination revealed tenderness and a small fixed mass in the right lower quadrant. At laparotomy a small curled-up appendix covered with omentum and adherent to the lateral wall of the pelvis was found. When the adhesions were separated a small amount of pus was found. There was no involvement of the cecum or lymphatic glands. Pathologic examination revealed tuberculosis of the appendix. The patient made a good recovery and was well to the time of the report. There was no pulmonary tuberculosis.

CASE 2.—A woman, aged 31, complained of frequent shooting pains in the right lower quadrant of the abdomen. Examination revealed tenderness near McBurney's point, with a small fixed mass near the right anterosuperior spine. Laparotomy revealed a small curled-up appendix adherent to the parietal peritoneum, covered with omental adhesions which, when separated, revealed a few drops of pus. The cecum and lymphatic glands appeared normal. The pathologic report was: tuberculosis of the appendix. There were no signs in the lungs. The patient was well following the operation to the time of the author's writing.

CASE 3.—The author described a third case but the specimen was lost.

Emmert (1918)[11].—A farmer complained of attacks of pain in the right lower quadrant of the abdomen, resembling appendicitis. He had pain in the right side on the least jarring. A roentgenogram of the chest revealed pulmonary tubercu-

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9. Porter, M. F.: J. Indiana State M. A. **6**:113, 1913.

10. Wilkins, G. C.: Tr. New Hampshire M. Soc. **126**:80, 1917.

11. Emmert, M.: Nebraska M. J. **3**:62, 1918.

losis. The appendix was removed, and the patient recovered and was well thereafter. A pathologic report showed that the appendix was tuberculous.

Gatewood (1920)[12].—A man, aged 39, complained of recurrent attacks of pain in the right lower quadrant of the abdomen. Examination of the chest gave negative findings. A mass was suspected in the right lower quadrant; there were tenderness and rigidity on deep palpation. Laparotomy revealed that the omentum and ileum were bound down to the appendix and cecum. The cecum felt infiltrated. Appendectomy was performed. The pathologic diagnosis was: hyperplastic tuberculosis of the appendix.

Warwick (1920)[13].—Case 1.—A man, aged 26, complained of recurring, almost daily, attacks of pain in the right lower quadrant of the abdomen, associated with diarrhea. Examination revealed apical tuberculosis and tenderness in the right lower quadrant. Appendectomy was performed, and the patient recovered. The pathologic report showed an ulcerative type of tuberculosis of the appendix. The patient was readmitted to the hospital seven months later with generalized anasarca and died seventeen days later. Postmortem examination revealed general edema, hydrothorax, ascites, thrombosis of the right internal jugular and subclavian veins, chronic adhesive pericarditis with marked dilatation of the right ventricle and tuberculosis of the intestines and the apexes of the lungs.

Case 2.—A woman, aged 29, complained of attacks of pain in the right lower quadrant of the abdomen. Active pulmonary tuberculosis was present, with positive sputum. There were tenderness and rigidity in the right lower quadrant. Pararotomy revealed that both the cecum and the appendix were markedly thickened and surrounded by closely adherent omentum. The appendix was removed, and the patient made an uneventful recovery. The pathologic report showed an ulcerative type of tuberculosis of the appendix.

Case 3 (from St. Joseph's Hospital).—A man, aged 37, complained of pain in the right lower quadrant of the abdomen. The family and personal history were negative for tuberculosis. Laparotomy revealed a long appendix, which was hard and stiff, and numerous granulations scattered over the area. The cecum was normal. The patient recovered. The pathologic report was: hyperplastic tuberculosis of the appendix.

Beck (1920)[14].—A woman, aged 22, complained of general weakness and loss of weight. Examination revealed a normal heart and normal lungs. There was nothing abnormal in the abdomen, but vaginal examination revealed salpingo-oophoritis, which was diagnosed as tuberculosis of the adnexa. Laparotomy revealed that the middle portion of the appendix had sloughed out. There were tubercles over the tip of the appendix and on the tubes and ovaries, which were involved secondarily. The appendix and adnexa were removed. The patient recovered rapidly under roentgen treatment. The pathologic report was: tuberculosis of the appendix and adnexa.

Noehren and Mueller (1922)[5].—A woman, aged 31, with active pulmonary tuberculosis, complained of pain in the right lower quadrant of the abdomen. Examination revealed tenderness and a mass in the right lower quadrant. Laparotomy revealed a swollen, congested appendix, with some injection of the surrounding peritoneum. No signs of tuberculosis were visible grossly in the intestines, cecum and peritoneum. The tubes and ovaries were normal. The appendix was removed.

12. Gatewood, G.: S. Clin., Chicago **4**:809, 1920.

13. Warwick, M.: Ann. Surg. **71**:139, 1920.

14. Beck, C.: S. Clin., Chicago **4**:1263, 1920.

The patient made an uneventful recovery and was discharged on the ninth day following the operation. The pathologic report was: tuberculosis of the appendix, with acute exacerbation.

Perrin and Dunet (1922)[15].—A girl, aged 15½ years, complained of pain in the right lower quadrant of the abdomen. There was no history of tuberculosis in the family. Examination revealed tenderness in the right lower quadrant, with some voluntary rigidity. Pelvic examination revealed a mass in the right side. Laparotomy revealed a short, very wide appendix. The other abdominal contents were normal. The appendix was removed. Recovery was uneventful. The pathologic report was: hyperplastic tuberculosis of the appendix, with acute inflammation and abscess formation.

Razzaboni (1925)[16].—CASE 1.—A youth, aged 17, complained of abdominal cramps and alternating periods of constipation and diarrhea Examination of the lungs revealed tuberculosis; the abdomen was distended and fluid was palpable. A diagnosis of tuberculous peritonitis with ascites was made. Laparotomy revealed a large amount of fluid. A mass was found in the lower part of the abdomen on the right, made up of the cecum and appendix covered with tubercles. The appendix was 10 cm. long and felt hard. The author was sure that this was a hyperplastic type of tuberculosis of the appendix. The abdomen was closed in layers without removal of the appendix, and the patient made an uneventful recovery.

CASE 2.—A man, aged 38, complained of a mass in the lower part of the abdomen on the right, which was becoming rapidly larger. Examination revealed apical tuberculosis on the left side. The abdomen was enlarged, and there was a large inguinoscrotal hernia on the right side. A diagnosis of tuberculous peritonitis, with concomitant right inguinoscrotal hernia, was made. Laparotomy revealed a large hernial sac containing the small intestine, cecum and appendix covered with tubercles. The appendix was thick and firm, and Razzaboni believed the condition to be due to a hyperplastic tuberculous process. A Bassini operation was performed, and the patient was discharged after spending a short time in the hospital. Shortly after, tuberculous meningitis developed, and the patient died. Permission for necropsy was not obtained.

Coley (1928)[17].—A man, aged 23, complained of pain in the right lower quadrant of the abdomen, of four months' duration. Examination revealed apical tuberculosis on the right and tenderness, rigidity and a palpable mass in the right lower quadrant of the abdomen. Laparatomy revealed a mass consisting of the cecum, appendix and omentum and enclosing an abscess cavity containing 1½ ounces (15.6 Gm.) of pus. The appendix was thickened and covered with fibrin. Near the cavity a pouchlike diverticulum of the terminal ileum was found, the distal portion of which had a hemorrhagic appearance. The remainder of the abdomen was normal. The appendix and diverticulum were removed, and the abdomen was drained. The pathologic diagnosis was: tuberculosis of the appendix, with acute suppurative periappendicitis and tuberculous diverticulum of the ileum. The patient was transferred to the ward for tuberculosis on the twenty-first day and died of pulmonary and enteric tuberculosis two months after operation.

Corvese (1925)[18].—A woman, aged 21, complained of amenorrhea, but examination resulted in a tentative diagnosis of tuberculous peritonitis. About five months

15. Perrin, E., and Dunet, C.: Presse méd. **30**:809, 1922.

16. Razzaboni, G.: Riforma med. **41**:965, 1925.

17. Coley, B. L.: Tuberculosis of Meckel's Diverticulum Associated with Tuberculous Appendix, Arch. Surg. **11**:519 (Oct.) 1925.

18. Corvese, A.: Rhode Island M. J. **8**:125, 1925.

later she had an attack of abdominal pain. Examination revealed tenderness and rigidity in the right lower quadrant of the abdomen, with marked distention. Laparotomy revealed a large amount of serous fluid in the abdomen; the appendix was gangrenous and adherent and had an abscess at its base. Appendectomy was performed, and drainage was instituted. The patient was discharged on the fifteenth day but drainage continued for seven months. The appendix was tuberculous, with an acute superimposed inflammation.

Popper (1926) [19].—A youth, aged 20, who suffered from pulmonary tuberculosis, complained of abdominal pain which came and went and which at times was severe. Examination revealed a tender mass near the umbilicus. Laparotomy revealed a long appendix covered with fibrin and some congestion of the cecum. There was no evidence of pathologic changes in the rest of the abdomen. The patient made an uneventful recovery. The pathologic report was: tuberculosis of the appendix, with superimposed acute inflammation.

Vergely (1927) [20].—A woman, four months pregnant, complained of pain in the epigastrium after meals and vomiting. Roentgen examination showed deformity of the pyloric cap. Consultation resulted in a diagnosis of pyloric ulceration, with possible appendicitis. She was given medical treatment to allay the attacks. Five months later she gave birth to a normal female child. About two months later laparotomy was performed. All the abdominal viscera were normal except the appendicular and cecal serosa, which were seeded with tubercles. The appendix was removed. The patient recovered. She had had an infiltration of the apex of the left lung during the pregnancy and shortly after the operation, but this had completely disappeared three months after the operation. Microscopic examination confirmed the tuberculous condition of the appendix.

Molfino (1927) [21].—A girl, aged 17, complained of repeated attacks of pain in the abdomen, which were localized in the right lower quadrant. Laparotomy was performed in May, 1926, and nothing abnormal was found. She continued to have attacks of pain, and a diagnosis of adnexal disease was made. Five months after operation, examination revealed large tender adnexa on the right side. Laparotomy at this time disclosed tuberculosis of the fallopian tubes, ovaries, cecum, terminal part of the ileum and the appendix. Both fallopian tubes and the right ovary were removed. The appendix was not removed, because of the dense adhesions binding it down closely to the cecum. The patient made an uneventful recovery. The pathologic report on the fallopian tubes and right ovary showed tuberculous infection.

Perera (1927) [22].—A girl, aged 19, complained of abdominal pain which recurred at irregular intervals. Examination revealed chronic pulmonary congestion and a tender mass over the appendix. Laparotomy revealed a large, thick but short appendix, with tuberculous granulations. The appendix was removed. The patient recovered and was well two years later.

Pfeiffer and Smyth (1928) [23].—A woman, aged 26, complained of marked diarrhea and loss of weight. There was a history of pulmonary tuberculosis, which had never been very active. Examination led to a diagnosis of colitis of *unknown*

19. Popper, H.: Wien. med. Wchnschr. **79**:478, 1929.
20. Vergely, J.: J. de méd. de Bordeaux **57**:20, 1927.
21. Molfino, A. H.: Semana méd. **1**:1534, 1927.
22. Perera, A.: Med. ibera **2**:125, 1927.
23. Pfeiffer, D. B., and Smyth, C. M., Jr.: S. Clin. North America **8**:877, 1928.

origin. Cecostomy was performed through a McBurney incision. The appendix was found to be red, thick and studded with tubercles, and a small amount of clear straw-colored fluid was found in the abdomen. There was also a mass about the size of a small lemon in the cecum near the base of the appendix. The appendix was removed. The pathologic report was tuberculosis. Postoperatively the patient was treated with irrigations of silver nitrate through a catheter sewed into the cecum. She also had treatment with ultraviolet rays and general care for eighteen months. She gained 45 pounds (20.4 Kg.), her weight increasing from 60 to 105 pounds (from 27.2 to 47.6 Kg.). Closure of the cecum was performed. No evidence of tuberculosis was found intra-abdominally, and the mass in the cecum had disappeared. The patient made an uneventful recovery.

Vargas (1929)[24].—A boy, aged 11 years, complained of attacks of pain in the right lower quadrant of the abdomen. These attacks recurred several times until he had a very severe attack, and he was brought to the hospital. The Pirquet reaction was positive. Laparotomy revealed an appendix studded with tubercles and bound down to the cecum. There was inflammation of the appendix, which also involved the cecum. No lesions of the intestines or peritoneum were found. The patient made an uneventful recovery. The pathologic report was tuberculosis of the appendix.

Askey (1929)[25].—A man, aged 27, complained of sudden pain in the lower part of the abdomen on the right, accompanied by nausea. Three days later, on seeing a physician, he was told that the condition was appendicitis. He continued to have pain in the right side for the next two months. At the end of this time examination revealed a tender, movable mass in the right lower quadrant. Laparotomy revealed a swollen appendix, with a small perforation near the base through which a grass stalk protruded. The cecum and the rest of the abdomen were normal. The patient made an uneventful recovery. The pathologic report was: tuberculosis of the appendix. Examination showed a normal heart and normal lungs.

Bloch and Mayer (1929)[26].—A woman, aged 31, complained of sterility and scanty menstrual periods for the past two years. Examination revealed a retroverted uterus. Laparotomy revealed miliary tubercles covering the adnexa, the ileocecal region and the appendix. The peritoneum and the rest of the abdomen were normal. The appendix was removed. The postoperative course was uneventful. The physician did not remove the involved adnexa because he believed that the seat of the tuberculous process was already in the abdomen and that the operation might disseminate the bacilli or cause the process to flare up.

P. Muller (1929)[27].—A woman, aged 25, complained of recurring attacks of pain, which were especially marked in the right lower quadrant of the abdomen. Examination of the chest gave negative findings. There was tenderness on the right side of the abdomen. Pelvic examination revealed tender, slightly enlarged adnexa. Laparotomy showed adhesions of the uterus to the sigmoid and rectum. The ovaries were adherent to the broad ligament and the pelvic brim. The appendix was atrophied at the tip and broad at the base. Hysterectomy and appendectomy were performed. The pathologic report was: tuberculosis of the adnexa and appendix. The patient made an uneventful recovery.

24. Vargas, M.: Vida nueva **23**:207, 1929.

25. Askey, J. M.: California & West. Med. **30**:46, 1929.

26. Bloch, J. C., and Mayer, M.: Bull. Soc. d'obst. et de gynéc. **18**:321, 1929.

27. Muller, P.: Bull. et Soc. de chir. de Paris **21**:259, 1929.

Mason (1929)[28].—A man, aged 23, complained of pains in the lower part of the abdomen on the right and vomiting. Examination revealed pulmonary tuberculosis and tenderness in the right lower quadrant of the abdomen. Laparotomy revealed a long coiled and inflamed appendix, which was removed. The remainder of the abdomen was normal, except for enlarged lymphatic glands at the ileocecal angle. Pathologic examination revealed tuberculous appendicitis, with acute inflammation. The patient was later transferred to a sanatorium.

de Almeida Prado (1930)[29].—A youth, aged 18, was admitted to the hospital, complaining of pain in the abdomen, rectal tenderness and loss of weight. Examination revealed that the heart and lungs were normal; the abdomen was distended and tender. Roentgen examination revealed adhesions between the sigmoid and the appendix. Laparotomy revealed chronic tuberculous appendicitis and cicatricial mesosigmoiditis. Postoperatively the patient was given general treatment and ultraviolet irradiation.

Robles (1930)[30].—A girl, aged 17, who suffered from pulmonary tuberculosis and who was being treated by artificial pneumothorax, complained of severe pain in the right side of the abdomen. Appendectomy was performed. She made an uneventful recovery and was discharged from the hospital within eleven days. The pathologic report was: tuberculosis of the appendix.

Carnelli (1931)[31].—A man, aged 27, complained of pain in the abdomen, with alternating periods of constipation and diarrhea. Examination of the chest gave normal findings. The abdomen was distended and was tender and rigid on the right side, with a suggestion of a mass. Laparotomy revealed a long, inflamed appendix studded with tubercles, with free fluid in the peritoneal cavity. The rest of the abdomen showed no abnormality. The appendix was removed. Recovery was uneventful, and the patient was well after three years. The pathologic report was: primary hypertrophic tuberculosis of the appendix.

Stiles (1931)[32].—A youth, aged 19, complained of pain in the right lower quadrant of the abdomen, with nausea, which began two days prior to admission to the hospital. Examination revealed tenderness, rigidity and a palpable mass in the right lower quadrant. Laparotomy revealed an inflammatory mass on the right side, made up of omentum wrapped around the inflamed cecum. The appendix was not visualized. Resection of the entire ileocecal region and ileocolic anastomosis were performed. The postoperative course was uneventful. The pathologic report indicated hyperplastic tuberculosis of the appendix and cecum. Roentgen examination of the chest gave negative findings for tuberculosis.

Sanguily Quintana (1931)[33].—A woman, aged 29, complained of a sensation of heaviness in the abdomen, difficult defecation, leukorrhea and loss of weight. Examination of the apex of the left lung revealed tuberculosis and a distended tender abdomen. Pain was especially marked over McBurney's point. Pelvic examination revealed a retroverted uterus and tender adnexa. Laparotomy was performed, and a Baldy-Webster suspension of the uterus was done, as well as salpingectomy and appendectomy. Pathologic examination showed tuberculous appendicitis.

28. Mason, G. A.: Newcastle M. J. **9**:122, 1929.
29. de Almeida Prado, A.: Ann. Fac. de med. de São Paulo **5**:311, 1930.
30. Robles, A. A.: Rev. Soc. de med. int. y Soc. de tisiol. **6**:577, 1930.
31. Carnelli, R.: Arch. ital. di chir. **30**:158, 1931.
32. Stiles, C. D., Jr.: South. M. J. **24**:958, 1931.
33. Sanguily Quintana, J.: Vida nueva **28**:209, 1931.

Finzi (1932)[34].—A man, aged 24, was operated on for appendicitis in August, 1927. The postoperative course was uneventful. Two years later the patient returned with a palpable mass in the right side of the abdomen. Laparotomy revealed ileocecal tuberculosis. Ileocecocolic resection and lateral ileotransversostomy were performed. The patient made an uneventful recovery. Pathologic examination confirmed the diagnosis of ileocecal tuberculosis, and on careful study of the appendix removed two years previously hypertrophic tuberculosis was found.

Primary tuberculosis of the appendix must be very rare. While its existence cannot be denied theoretically, so far as we know, there is only 1 case on record (Beck [14]) in which, after the patient died subsequent to removal of a tuberculous appendix, autopsy failed to reveal any other tuberculous lesion, with exception of involvement of the lymph nodes in the ileocecal region. However, a latent microscopic or old healed focus or a microscopic lesion in the lymph nodes might have been overlooked. In this connection, an appendix removed either as a routine or by design and found to be tuberculous only after microscopic examination may afford the first information as to the presence of this disease in the body and the patient subsequently may show other lesions. With this in mind, the following case is offered:

Koster Clinic.—CASE 1.—E. H., a woman, aged 23, was admitted to the hospital on Oct. 9, 1931, complaining of pain in the lower right quadrant of the abdomen.

Six years before admission she began to have dull pains in the right lower quadrant of the abdomen. These pains were intermittent but not severe and continued until two weeks before admission, when they began to be severe and cramplike. They radiated to the lower part of the back and the right thigh and were aggravated if the patient walked or rested her weight on the right side. The patient also had a white, watery vaginal discharge and nausea when these pains became more severe. Menstruation had been regular; the patient had begun to menstruate at the age of 13; the periods occurred every twenty-eight days and lasted four days. Three months before admission a physician inserted a hard rubber pessary for the retroversion of the uterus. The past history and family history were negative. The patient was not married.

Physical examination revealed a young white adult female, well nourished and well developed, who did not appear acutely ill. The head and neck were normal. There was equal expansion on both sides of the chest, the lungs were clear, and the breath sounds were normal. The heart sounds were regular, and there were no murmurs.

There was some tenderness in the right lower quadrant of the abdomen, especially over McBurney's point, radiating to the epigastrium. There was slight tenderness in the left lower quadrant. No spasticity or masses were palpable in the abdomen. Murphy's sign was absent. The extremities and the reflexes were normal.

Rectal examination revealed a retroverted uterus and some tenderness on the right side. No masses were palpable. The temperature was 99 F.; the pulse rate was 90 and the respiratory rate 22 per minute.

The laboratory reported that the urine showed a trace of albumin, but no sugar, and a few white blood cells microscopically. The hemoglobin was 82 per cent.

34. Finzi, O.: Boll. e mem. Soc. piemontese di chir. **2:**986, 1932.

The red blood cells numbered 4,300,000 per cubic millimeter; the white blood cells, 10,800, with 70 per cent polymorphonuclears, 16 per cent lymphocytes and 12 per cent monocytes.

A diagnosis of chronic appendicitis and retroverted uterus was made.

The next day laparotomy was performed under spinal anesthesia. The liver was ptosed to the level of the umbilicus; the gallbladder and stomach appeared normal. The uterus was retroverted, and the appendix, which was bulbous, was bound down by firm adhesions to the cecum. There were a few fine adhesions in the posterior culdesac; these were cut. A Simpson-Gilliam suspension of the uterus and appendectomy were performed. The abdomen was closed in layers.

The patient made an uneventful recovery. Microscopic examination of the appendix showed tuberculosis. Roentgenologic study of the chest revealed no signs of tuberculosis. The patient was discharged on October 21.

From an operative and clinical standpoint, this case is one of primary tuberculosis of the appendix. To the time of writing the patient has not presented any other evidence of a tuberculous lesion. Beck,[14] in 1920, reported a case of tuberculosis of the appendix with extension to the fallopian tubes and the ovaries, in which there were no other abdominal or pulmonary signs of tuberculosis. He reported this case as one of primary tuberculosis of the appendix.

The following two cases are clinically typical of acute appendicitis:

CASE 2.—M. A., a girl, aged 17, was admitted to the hospital on June 26, 1931, complaining of pain in the lower part of the abdomen on the right and nausea.

The illness began three days prior to admission, when she was seized with generalized abdominal cramps. She was nauseated at the time of admission but did not vomit. About twenty-four hours after the onset the pain became localized in the lower part of the abdomen on the right.

The family history was negative, except that the brother of the patient's father had active pulmonary tuberculosis. The patient had had scarlet fever, measles, whooping cough and influenza. Tonsillectomy was performed in 1926. Menstruation began at the age of 13; the periods occurred every twenty-eight days and lasted three days.

The patient appeared acutely ill. The chest showed equal expansion on both sides. The breath sounds were normal, and no râles were heard. The heart sounds were regular, with no murmurs. There were tenderness and rigidity in the entire lower part of the abdomen; these were more marked in the right lower quadrant. Tenderness on release of pressure in the left lower quadrant was referred to the right lower quadrant. Murphy's sign was absent.

Rectal examination revealed a tender mass high on the right side.

Examination of the urine gave negative results. The red blood cells numbered 4,000,000 per cubic millimeter, with hemoglobin 86 per cent. The white blood cells totaled 13,400, with 84 per cent polymorphonuclears and 16 per cent lymphocytes.

A diagnosis of appendicular abscess was made. Laparotomy was performed under spinal anesthesia. An acutely inflamed abscessed appendix was found walled off by omentum and by the cecum and ileum. The diameter of the appendix at the base was 1⅛ inches (2.8 cm.), while the length was 3 inches (7.6 cm.). Appendectomy was performed. A cigaret drain was inserted to the pelvis, and the abdomen was closed in layers.

The patient made an uneventful recovery. The wound drained profusely for about nine days, then healed rapidly.

The pathologic report was: tuberculosis of the appendix, with acute purulent inflammation. A roentgenologic study of the chest revealed no signs of tuberculosis. The patient was discharged on July 12.

Askey,[25] in 1929, reported a case in which a diagnosis of appendicular abscess was made. Laparotomy revealed a walled-off appendicular abscess with a perforation at the tip containing a grass stalk. Microscopic examination revealed tuberculosis of the appendix.

Similarly, in our case we had no idea that we were dealing with primary tuberculosis of the appendix until microscopic examination revealed it. The next case reported is similar:

CASE 3.—J. R., a boy, aged 14, was admitted to the hospital on Sept. 27, 1930, complaining of pain in the lower part of the abdomen on the right, with nausea and vomiting.

The illness began the day before admission, when the patient was suddenly seized with generalized abdominal cramps. He also became nauseated and vomited three times. The same night the pain became localized in the right lower part of the abdomen.

The family history was negative. The patient had measles when he was 6 years old. He stated that he had had some uneasiness in the lower part of the abdomen on the right during the month prior to admission. He appeared to be acutely ill. The chest revealed equal expansion on both sides. The lungs were clear, and no abnormal sounds were heard. The heart sounds were regular, and there were no murmurs.

There were tenderness and rigidity in the right lower quadrant of the abdomen. No tenderness on rebound was present. There was no Murphy's sign. Rectal examination gave negative results, except for some tenderness on the right side. The extremities and the reflexes were normal. The temperature was 100 F.; the pulse rate was 112 and the respiratory rate 20 per minute. Examination of the urine gave negative results.

The red blood cell count was 4,600,000, with hemoglobin 92 per cent. The white blood cells totaled 14,000, with 82 per cent polymorphonuclears and 18 per cent lymphocytes.

A diagnosis of acute appendicitis was made. Laparotomy was performed under spinal anesthesia; it revealed acute suppurative appendicitis. The appendix was bound down by adhesions to the cecum and covered by lightly adherent omentum. Appendectomy was performed. The postoperative course was uneventful. The temperature, pulse rate and respirations were normal within forty-eight hours after operation and remained so until the patient's discharge from the hospital on October 8. A few days prior to his discharge, following a pathologic report of tuberculosis of the appendix, roentgenologic study of the chest revealed no pulmonary involvement.

Since in cases 2 and 3 there was no clinical or roentgenographic evidence of tuberculosis nor any signs of tuberculosis within the peritoneal cavity visible to the surgeon, the condition in both these cases might be considered, from a clinical standpoint at least, as primary appendicular tuberculosis, bearing in mind that at some future date a lesion may appear that was not demonstrable at the time of writing.

The fourth case is one of frank pulmonary tuberculosis complicated by tuberculosis of the appendix.

CASE 4.—H. L., aged 31, was admitted to the hospital on May 30, 1930, complaining of pain in the right lower quadrant of the abdomen. Three weeks prior to admission he began to have sharp cramplike pains in the lower part of the abdomen on the right, which did not radiate anywhere but remained localized in that area. The pains became worse until the day of admission, when they were so severe that the patient was unable to walk.

The chest presented equal expansion on both sides. The breath sounds in both apexes were bronchovesicular, and a few subcrepitant râles were heard. The heart beat was regular, and no murmurs were present. There was tenderness in the right lower quadrant of the abdomen, which was more marked over McBurney's point. There was no rigidity and no mass was palpable. Murphy and psoas signs were not present. No tenderness on release of pressure was present. Rectal examination gave negative results. The temperature was 99 F.; the pulse rate was 98 and the respiratory rate 20 per minute.

Laboratory reports revealed negative results of urinalysis, except for a faint trace of albumin. The red blood cell count was 5,450,000, with hemoglobin 100 per cent. There were 10,150 white blood cells, with 72 per cent polymorphonuclears, 24 per cent lymphocytes and 4 per cent monocytes.

A diagnosis of subacute appendicitis and pulmonary tuberculosis was made.

Laparotomy was performed under spinal anesthesia. An acutely inflamed appendix was found bound down to the lateral pelvic wall by firm adhesions and covered with omentum. The ileum was loosely adherent to the base of the appendix. The other abdominal viscera appeared normal. Appendectomy was performed without drainage. On the second postoperative day the patient began to cough up a frothy, blood-stained sputum. His temperature was 100.4 F.; the pulse rate was 96 and the respiratory rate 22 per minute. Examination of the chest revealed dulness in the apex of both lungs and fine subcrepitant râles. Both bases were clear. The next day the patient had typical prune juice sputum and was coughing moderately. His temperature rose to 102.2 F., with a pulse rate of 120, but respirations remained at 22 per minute. The sputum was negative for tubercle bacilli.

The patient's condition seemed fair until the ninth day after the operation, when he coughed so hard that his wound opened and a small loop of ileum was eviscerated. This was replaced in the abdomen, and the wound was tightly strapped with adhesive tape. The next day the patient's condition appeared to be poor. Examination of the chest revealed many moist râles, with bronchial and bronchovesicular breathing from the apex to the base of the lung on the right side and from the apex to the inferior angle of the scapula on the left.

The base of the left lung showed flatness and absence of breath and voice sounds—all evidence of effusion. The heart was enlarged to the left about 1 cm. outside the midclavicular line. The sounds were of poor quality. Examination of the sputum showed Bacillus tuberculosis. Unquestionably, the pulmonary lesion at this time was acute tuberculous pneumonia. The patient's condition became progressively worse, and death occurred on July 12 at 1:50 p. m.

The pathologic report on the condition of the appendix was: "caseating tuberculosis."

COMMENT

From a pathologic standpoint, the lesions confined to the appendix may be divided into two types: (1) the ulcerative and (2) the hyperplastic. The former is by far the more common. Grossly, the appearance of the appendix may vary from that of a seemingly normal organ with perhaps slight congestion of the superficial capillaries to that of an organ showing all the signs of actively acute inflammation. The walls may be slightly thickened, and the serosa may show small tubercles or even a thin plastic exudate on the surface. Gross ulceration of the mucosa may occur, resulting in a greater or lesser loss of substance.
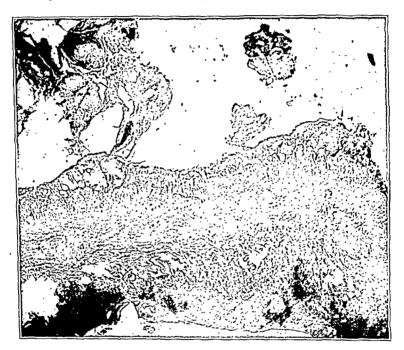
Fig. 1.—Section of the wall of the appendix with a thin mucosa without folds. The serosa is slightly thickened. There are some adhesions, which show some nodular aggregation of granulation tissue with a lighter center. Low power magnification.

The base of an ulceration may show extensive caseous material. In other cases the floor of the ulcer may show minute grayish tubercles. The ulceration of the mucosa may extend into and through the submucosa and in some instances even through the muscular coat to such an extent that nothing may be left of the latter, the remainder of the wall being only serosa. In the event that attempts at healing are successful, the ulcerative surfaces become adherent, and the organ becomes either strictured or obliterated. Microscopically, the mucosa and submucosa show the most extensive involvement, although, as has been said

before, the musculature may also suffer considerably, the lesion appearing in the form of discrete tubercles or extensive ulcerations and necrosis, with the characteristic epithelioid and giant cells around an area of caseation. In the earlier stages the ulceration is more likely to occur either at the tip or at the base of the organ. If the ulceration becomes advanced it may even extend through the serosa, with resultant perforation, following which any of the sequelae of perforative appendicitis may develop.

The hyperplastic type of tuberculous appendicitis is much more rare. It is characterized by a very large appendix with a thickened wall,

Fig. 2.—Serosa of the appendix, showing granulation tissue extending slightly to the outer muscular coat. The granulation tissue encloses groups of epithelioid cells and several giant cells of the Langerhans type.

marked proliferation of connective tissue and complete or relative absence of caseation. The walls become markedly increased in thickness, and occasionally the organ may become so large as to be palpable through the abdominal wall, in which event it may be mistaken for a neoplasm. The hyperplasia of the connective tissue and the contraction which it undergoes may not be entirely uniform, causing irregularities in the shape of the organ. The walls become rigid, and the lumen may show a tendency toward obliteration. While, on superficial examination it may be mistaken for a neoplasm, the differentiation should not be difficult on close inspection.

On microscopic examination, the mucosa is usually found to be intact. Instead of being destructive as in the ulcerative type, the lesion is, as the name implies, a hyperplastic one, consisting most frequently in marked thickening of the muscular coat as a result of a deposition of large amounts of connective tissue and lymphoid infiltration. The submucosa may show some tubercles, but on the whole the typical picture is one of lack of ulceration and caseation, with a large amount of connective tissue reaction.

The secondary form of tuberculosis of the appendix is frequently associated with a tuberculous lesion of the intestines, particularly of the
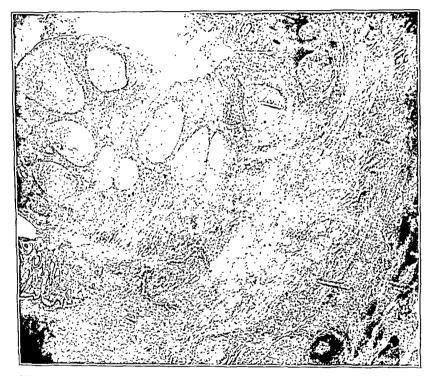
Fig. 3.—Hyperplastic mucosa with large follicles and unusually large secondary follicles. The submucosa and part of the muscularis is substituted by granulation tissue. There are numerous nodules which consist of epithelioid cells and which stain lighter than the adjacent area infiltrated with round cells.

cecum. Some authors, including Mayo, have gone so far as to state that it is practically always associated with the same infection in the latter. Then, too, most observers have had the experience of finding ileocecal or intestinal tuberculosis frequently, with no involvement of the appendix. These two findings suggest that the appendix is usually secondarily infected. It must be remembered, however, that whether the local infection occurs by extension or by the hematogenous route, the bacilli may be disseminated along the alimentary tract in many

places, with many foci developing simultaneously and yet with different degrees of rapidity. In addition to the obvious method of entrance of tubercle bacilli into the intestinal tract by the swallowing of contaminated sputum, there is also the possibility of the entrance of the organism in contaminated food. This includes not only infected milk but also infected butter and cheese. The latter type of infection is one explanation for the possible occurrence of primary tuberculosis (Schroeder and Cotton [35]). Regarding the other means by which the appendix may become infected, namely, by way of the peritoneum, the lymph stream and the blood stream, little can be said. That infection by such routes is theoretically possible cannot be denied, but evidence in favor of the transmission of the bacilli by these routes is not strong.

Clinically, the disease may manifest itself in two forms, the acute and the chronic. In the acute form differentiation from acute appendicitis of the ordinary variety is almost impossible. It may, of course, be suspected when the syndrome of acute appendicitis occurs in a patient who already has well developed tuberculous lesions elsewhere in the body, but in the absence of such a history there are no signs by means of which the tuberculous type of acute appendicitis can be differentiated from any other form. In the chronic form, which is far more frequently encountered, tuberculosis elsewhere in the body, a history of occasional attacks of diarrhea, the recognition of a mass in the region of the appendix without symptoms of abscess and, in children, hard muscular tumors in the abdomen which are not fecal masses are all signs which, in the presence of the ordinary symptoms of chronic appendicitis, might point to the tuberculous nature of the lesion. One other form of tuberculosis of the appendix is encountered clinically, namely, the latent form, in which the appendix which has been removed as a routine during the course of some other operation is found to be tuberculous on histologic examination. This type may never cause any symptoms.

White,[36] in a series of autopsies, noted several instances of acute and chronic tuberculous disease of the appendix in persons who had never shown any signs of appendicular disease during life. The general signs of the chronic variety of tuberculous appendicitis include a characteristic rise in temperature in the afternoon, with slight acceleration of the pulse rate, perhaps slight loss of weight and, in some instances, nocturnal perspiration. The chronicity is extreme, but there may be interruptions of acute exacerbations. Between these acute flare-ups there is a vague sense of discomfort in the right lower quadrant of the abdomen, with some tenderness. The clinical diagnosis should be suggested in the face of a history of chronic appendicitis with which there is associated a progressive loss of weight, rise in temperature in the

35. Schroeder, E. C., and Cotton, W. E., quoted by Eisendrath.[9]
36. White, J.: Ann. Rep. Henry Phipps Institute, 1906-1907 and 1907-1908.

afternoon, nocturnal perspiration and occasional attacks of diarrhea. The literature since Muller's [3] article contains little of value regarding the prognosis in tuberculous appendicitis. In only 8 of the 66 cases which he reviewed was it reported definitely that the patient was cured, but the report of these cures is of little value since the patients were followed for only a few months after operation. Muller noted that in 3 cases, one, two and three years, respectively, elapsed before death occurred from pulmonary tuberculosis. Ten patients were recorded as still suffering from some form of tuberculosis at the time of the report. One patient is said to have died as a direct result of the operation. Fifteen others died a short time after operation, and the final result is not stated in the remaining cases. If the disease is primary and if the operation is performed before secondary involvement occurs, there should be hope of a cure. Secondary tuberculosis of the appendix offers a poorer prognosis, especially when following pulmonary involvement and in the presence of a coincidental lesion. However, in one of Pauchet's [37] cases, in which the appendix was removed because of pain over the region, at which time the peritoneum was found to be studded with tubercles and the appendix also involved, laparotomy for incisional hernia performed some time later revealed a normal appearance of the peritoneum.

Pfeiffer and Smyth's [23] case, which is abstracted in this article, also showed complete disappearance of tuberculous lesions in the abdomen eighteen months after appendectomy and cecostomy at the time when the cecostomy opening was closed.

Regarding the treatment, little need be said. If the condition is acute, the appendix should be removed immediately, even in the presence of complicating pulmonary disease, under some form of anesthesia other than inhalation narcosis. The anesthesia of choice is the spinal. In the chronic type of the disease the condition of the lungs should determine the advisability of surgical intervention.

SUMMARY AND CONCLUSION

Up to December, 1917, 89 cases of tuberculosis of the appendix had been reported in the literature by Scott.[4] Three other cases before 1917 that were not included in the report are given in this article, followed by a complete abstract of 31 authentic cases reported from 1917 to the time of writing. To this number we have added 4 cases of our own which we found in 3,271 consecutive appendectomies. In 3 of our cases the condition was apparently primary tuberculosis of the appendix; in the fourth there was coexisting pulmonary tuberculosis. This article brings the total number of authentic cases of tuberculous appendixes reported in the literature to the end of 1932 up to 127.

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37. Pauchet, quoted by Petit, M.: Thèse de Paris, 1905, p. 71.

HEMORRHAGE AND SHOCK AS CAUSES OF DEATH FOLLOWING ACUTE PORTAL OBSTRUCTION

ROBERT ELMAN, M.D.

AND

WARREN H. COLE, M.D.

ST. LOUIS

√Although it has been known for nearly a century that acute obstruction of the portal vein, such as that produced by ligation or that occasionally occurring through thrombosis after biliary operations, is always followed in a short time by death, no satisfactory explanation of the fatal outcome has been offered. The first demonstration of the phenomenon is attributed to Oré,[1] who, in 1856, discovered that ligation of the portal vein in rabbits resulted in the death of the animals in a short time. It is interesting that Claude Bernard [2] at one time admitted a complete inability to offer an explanation, but several years later [3] expressed the theory that exsanguination, by stasis of blood in the intestinal tract, with a consequent fatal anemia might account for death. However, he offered no proof of that supposition, nor was he aware that Tappenheimer [4] had previously reported experiments which tended to disprove the idea.

In an effort to explain the cause of death following ligation of the portal vein we resorted to many different types of experiments.

EXPERIMENTAL PROCEDURES AND FINDINGS

Adult cats or dogs were anesthetized with ether or sodium amytal (about 75 mg. per kilogram of body weight, given intravenously), the abdomen was opened, and the portal vein was exposed at the hilus of the liver and ligated. Most of the animals were starved for from eighteen to twenty-four hours, but some were not. When blood pressure readings were taken, either the carotid or the femoral artery was connected with a mercury manometer and a continuous

1. Oré, quoted by Neuhof.[5]

2. Bernard, Claude: Leçons sur les propriétés physiologiques et les altérations pathologiques des liquides de l'organisme, Paris, J. B. Baillière et fils, 1858, vol. 2, p. 196.

3. Bernard, Claude: Leçons sur le diabète et la glycogenèse animale, Paris, J. B. Baillière et fils, 1877, p. 316.

4. Tappenheimer, H.: Ueber den Zustand des Blutstroms nach Unterbindung der Pfortader, Arb. a. d. Physiol. Anstalt, Leipzig 7:11, 1873.

tracing was obtained. Our experiments may best be described by considering them in separate groups:

1. *General Observations.*—The behavior of animals and the pathologic changes occurring as a result of ligation of the portal vein are constant and have been carefully described by Neuhof[5] and others. We observed few symptoms or signs which could not be explained on a basis of shock due to hemorrhage. The animal recovers slowly, if at all, from the effects of the anesthetic. If it regains consciousness, it appears to be desperately ill at all times and takes no interest in its surroundings. Extreme weakness is constantly observed; in fact it is so marked that the animal is compelled to maintain a recumbent position before it loses consciousness. The mucous membranes of the mouth are very pale. The pulse is of poor volume and tachycardia is usually present. Respiration may be variable, but the increased depth with rapid rate typical of air hunger resulting from hemorrhage is frequently seen. The blood pressure falls sharply within a
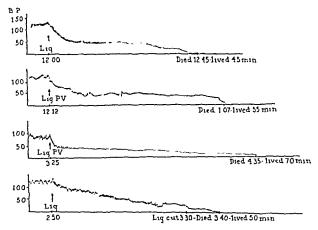
Chart 1.—Blood pressure tracings of four dogs following ligation *(Lig.)* of the portal vein *(P. V.)*, showing the sharp drop to "shock" level and death. In the lowest curve the ligature was cut in an effort to revive the animal, but this was done after irremediable changes had taken place.

few minutes after ligation and gradually decreases until death (chart 1). In a series of nineteen dogs on which portal ligation was performed the average duration of life was sixty-six minutes (table 1). The variations observed in the duration of life of starved or nonstarved animals, whether given ether or sodium amytal intravenously as an anesthetic, are so slight that they are probably of no significance. However, if the ligature is not placed high enough (i. e., proximally) to include the coronary and pancreaticoduodenal veins, or if the ligature is not absolutely tight, the duration of life may be prolonged considerably. At autopsy the spleen and the entire intestinal tract including the stomach, small bowel and large bowel are cyanotic, edematous and engorged with blood. The spleen is enlarged from three to six times. The serosa of the intestine loses its luster, but definite gangrene is not present. The wall of the intestine is firm

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5. Neuhof, Harold: Experimental Ligation of the Portal Vein: Its Application to the Treatment of Suppurative Pylephlebitis, Surg., Gynec. & Obst. **16**:481, 1913.

and thickened and microscopically is filled with red blood cells. The omentum and mesentery are likewise edematous. Numerous superficial and deep hemorrhages are encountered in the organs mentioned. Occasionally small amounts of bloody fluid are found in the lumen of the stomach and intestine. Scott and Wangensteen[6] noted that there is a considerable loss of blood and fluid into long loops of intestine experimentally strangulated. In some instances this loss is of sufficient magnitude to cause death.

2. *Toxicity of the Blood and Lymph.*—In a series of six dogs the thoracic duct was dissected and intubated, and lymph was collected for a control period before ligation of the portal vein and then afterward until the animal died. Just before death, samples of systemic blood and blood from the portal vein behind the ligature were also collected. Clotting was prevented by the use of sodium oxalate (10 mg. to 10 cc.). The clear plasma was then injected into guinea-pigs and white mice intraperitoneally in doses up to 3 cc. per hundred grams of weight. Without describing in detail these experiments it was apparent

TABLE 1.—*Duration of Life Following Ligation of the Portal Vein*

| | 19 Dogs | | | | 6 Cats | |
| | Ether Anesthesia | | Amytal Anesthesia | | Ether Anesthesia | |
	Starved	Not Starved	Starved	Not Starved	Starved	Not Starved
	90 min.	45 min.	95 min.	65 min.	60 min.	60 min.
	60 min.	60 min.	95 min.	30 min.	60 min.	
	60 min.	100 min.	45 min.	55 min.	35 min.	
	35 min.		35 min.		65 min.	
	55 min.		50 min.		60 min.	
	140 min.		35 min.			
	80 min.					
Average*	74 min.	68 min.	60 min.	57 min.	56 min.	60 min.

* The average for all the dogs was 66 minutes.

that none of the injected material proved toxic; and when it was, there was no essential difference over the controls.

3. *Increase in Weight of the Splanchnic Area.*—Another series of dogs and cats was operated on in pairs, one serving as a control, the other dying about one hour after ligation of the portal vein, at which time the control was killed. The entire gastro-intestinal tract was removed from each and weighed to determine how much blood was lost in the splanchnic area. These experiments have been reported previously,[7] and it need only be mentioned here that the increase in weight of the stomach, intestine and spleen in the animals with occlusion of the portal vein—due presumably to the entrapped blood—is great enough to account for the fatal outcome on the basis of loss of blood from the systemic circulation alone. Thus in the dogs this loss of blood, as shown by the increased weight of the gastro-intestinal tract, is 5.2 per cent of the body weight; in cats

6. Scott, H. G., and Wangensteen, O. H.: Blood Losses in Experimental Intestinal Strangulations and Their Relationship to Degree of Shock and Death, Proc. Soc. Exper. Biol. & Med. **29:**748, 1932.

7. Elman, Robert, and Cole, W. H.: Loss of Blood as a Factor in Death from Acute Portal Obstruction, Proc. Soc. Exper. Biol. & Med. **29:**1122, 1932.

it is 3.4 per cent. These figures exceed the amount of blood necessary to cause death by hemorrhage alone.[5]

4. *Effects of Transfusion.*—Efforts to combat loss of blood, or more correctly loss of fluid, after ligation of the portal vein almost always result in the prolongation of the life of the animal. As would be expected, the most efficient procedure is the transfusion of blood. For a limited time the intravenous injection of physiologic solution of sodium chloride is efficient in raising the low blood pressure. Injection of a solution of acacia produces a greater improvement, but the effect is poorly sustained. One must emphasize the fact, however, that even when transfusion of blood is used to combat the shock following the ligation it must be given before the animal becomes moribund. It is a fact well known in clinical experience that supportive measures to combat the shock of hemorrhage must be instituted shortly after shock ensues in order to prevent a high mortality. In the present experiments (table 2), for example, after ligation of the portal vein the average duration of life of six consecutive animals, which

TABLE 2.—*Effect of Transfusion of Blood on "Shock" Following Ligation of the Portal Vein*

	Number	Weight of Animal	Duration of Life	Amount of Blood, Cc.
Flow of blood not constant..	1	2.7 Kg.	2 hrs., 15 min.	275
	2	4.0 Kg.	2 hrs., 15 min.	330
	3	8.0 Kg.	3 hrs., 30 min.	850
	4	12.0 Kg.	3 hrs.*	1,100
	5	6.0 Kg.	1 hr.	200
	6	3.4 Kg.	2 hrs., 20 min.	450
Average duration of life, 2 hours, 23 minutes				
Flow constant, maintaining the blood pressure above the critical level of from 50 to 60 mm.	7	5.8 Kg.	7 hrs.*	1,050
	8	8.7 Kg.	3 hrs., 30 min.	1,490
	9	3.6 Kg.	5 hrs.	950
	10	5.4 Kg.	7 hrs., 30 min.*	1,250
Average duration of life, 6 hours, 15 minutes				

* The animal lived an unknown length of time beyond the figure specified.

were given a transfusion carelessly with an inconstant flow of blood, could be prolonged only to two hours and twenty-three minutes. We noted moreover, that if the blood pressure had been in the shock level for a half hour or more, and transfusion was neglected until the blood pressure fell below the critical level (say 40 mm. of mercury) even for a few minutes, we could not prevent death in spite of the transfusion of large quantities of blood. Similarly, if the ligature of the portal vein were cut too late, recovery could not occur (chart 1, lowest curve). Apparently certain vital organs such as the brain perhaps suffer irremediable damage after the blood pressure drops below a certain level even for a short time. On the other hand if the flow of blood during transfusion is maintained constantly, beginning fifteen or twenty minutes after ligation of the vein, thus preventing a fall of pressure below a critical level, life can be maintained for many hours (average, six hours and fifteen minutes +), as is illustrated by the last four consecutive animals in table 2. Two of these animals were still alive when last seen seven hours and seven hours and one-half, respec-

8. Johnson, G. S., and Blalock, A.: Experimental Shock: IX. Study of Effects of Loss of Whole Blood, of Blood Plasma and of Red Blood Cells, Arch. Surg. **22**:626 (April) 1931.

tively after the ligation. (This experiment is graphically represented in chart 2.) From the standpoint of these experiments it is of no particular interest how much longer than seven hours an animal will live following ligation of the portal vein, because, by that time the factor of gangrene of the intestine enters as a complication. Invariably, when a considerable amount of blood is transfused into the animal following ligation of the portal vein, mucosal as well as serosal hemorrhages will occur and bloody fluid will be found in variable quantities in the lumen of the intestine and stomach and the peritoneal cavity. Quantities of bloody fluid will be passed by rectum. The rapid loss of blood in this manner, aided by the early effects of gangrene, probably explains the inability to keep these animals alive for twenty-four hours or longer. After intestinal hemorrhages are manifested to any considerable extent, death usually follows in a short time. Hemorrhage is probably aided by the fact that no tendencies to clotting are exhibited in the blood trapped behind the ligature. Tschernikoff[9] and his associates called attention to the delayed clotting time in the blood trapped in the portal system behind the ligature. In contrast, Krymholz[10] had previously noted a shortened clotting time of the systemic blood after ligation of the portal vein, especially as the animal approached death. Other observers[11] have noted similarly that following extensive hemorrhage the systemic blood
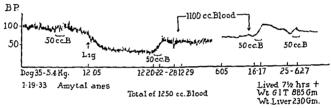
Chart 2.—Blood pressure tracing of one experiment mentioned in table 2. The usual fall in blood pressure is shown after ligation (*Lig.*) of the portal vein. Fifteen minutes later 50 cc. of blood was given, resulting in a sharp elevation. In all, 1,100 cc. of blood was given, with prolongation of life to over seven and a half hours. Compare this with the inevitable death in one hour when no transfusion is given (chart 1). *G.I.T.* indicates the gastro-intestinal tract.

clots much faster, and indeed it seems probable that the mechanism is the same in both cases. It appears to be a way nature has of aiding in "stopping the leak" by the formation of a clot more rapidly.

5. *Ligation of Splanchnic Arteries.*—When we discovered that the duration of life following ligation of the portal vein could be markedly increased by transfusion of blood, it seemed logical to assume that shock following ligation could be more readily prevented if at least some of the arteries supplying the portal system were ligated simultaneously with the portal vein. Accordingly, on two

9. Tschernikoff, A. M.; Malinjuk, W. W.; Jakubovitsch, M. I., and Klautaroff, M. C.: Zur Unterbindung der V. Portae, Arch. f. d. ges. Physiol. **227**:85, 1931.

10. Krymholz, M. L.: Experimenteller Beitrag zur Frage der Unterbindung der Pfortader (Einwirkung auf Druck und Gerinnungsvermögen des Blutes), Ztschr. f. d. ges. exper. Med. **67**:319, 1929.

11. Gray, H., and Lunt, L. K.: Factors Affecting the Coagulation Time of the Blood: V. The Effects of Hemorrhage, Am. J. Physiol. **34**:332, 1914.

occasions we ligated the superior mesenteric, inferior mesenteric, gastric and splenic arteries simultaneously with the portal vein. With transfusion of a small amount of blood one animal was alive when last seen at the end of six hours, and the other died at the end of six and one-half hours. • The amount of blood required to maintain a blood pressure compatible with life was 15 and 16 cc. per kilogram of body weight per hour, respectively, which, as will be noted in table 2, is less than one half as much blood as that required by the last four animals, which were given transfusions after ligation of the portal vein alone. The last four dogs with ligation of the vein alone required as much as 26, 38, 52 and 32 cc. of blood per kilogram of body weight per hour. Since some of the animals lived longer than the six or seven hour period of observation, it might seem difficult to draw conclusions as to the speed of progression of "shock." This is of course a source of error, but was the same in each series of animals, since one half of each group lived beyond the final hour of observation. The marked difference in the amount of blood required must therefore be very significant. In other words, when a large portion of the systemic blood is

TABLE 3.—*Ligation of the Aorta Alone (Above the Celiac Axis) as Compared with Simultaneous Ligation of the Aorta with the Portal Vein*

	Dogs Duration of Life		Cats Duration of Life	
	Ligation of Aorta Alone	Ligation of Aorta with Portal Vein	Ligation of Aorta Alone	Ligation of Aorta with Portal Vein
	6 hrs.*	6 hrs.*	3 hrs., 5 min.	3 hrs., 35 min.
	3 hrs., 15 min.	4 hrs., 15 min.	4 hrs., 5 min.	4 hrs., 20 min.
	5 hrs., 15 min.	1 hr., 45 min.	6 hrs.	4 hrs., 15 min.
	3 hrs., 10 min.	5 hrs., 45 min.	6 hrs., 30 min.	4 hrs., 30 min.
		5 hrs.		
		3 hrs.		
Average	4 hrs., 32 min.	4 hrs., 18 min.	5 hrs.	4 hrs., 10 min.

* The animal lived an unknown length of time beyond the figure specified.

prevented from entering the portal system by ligation of some of the arteries supplying it, it is much easier to keep the animal alive after ligation of the portal vein. This appears to be added evidence that the shock is due to hemorrhage and not to the production or absorption of toxic products.

We made no attempt to ligate all the arteries supplying the portal system, knowing that it would probably be impossible to find them, but more important, because the vessels beyond the ligature would probably be filled anyway through the many anastomotic channels. The presence of significant anastomotic vessels is supported and probably proved by Solowieff [12] who discovered that if the superior mesenteric, gastrosplenic and portal veins were ligated singly, at intervals of five or six days, the animal would not die. These results were verified by Neuhof.[5] Similarly, the slowly stenosing type of thrombosis of the portal vein seen clinically in hepatic cirrhosis fails to produce death, thereby adding support to the assumption that anastomotic vessels will form if the obstruction is not complete and is not produced instantaneously.

12. Solowieff, Alexander: Veränderungen in der Leber unter dem Einflusse künstlicher Verstopfung der Pfortader, Virchows Arch. f. path. Anat. **62**:195, 1875.

6. Ligation of the Aorta.—Knowing that ligation of the aorta above the celiac axis would probably prevent entirely the loss of blood into the splanchnic area trapped by the portal ligature, we performed a series of such experiments in dogs as well as cats. As can be seen in table 3, the average duration of life is almost the same in the dogs with ligation of the aorta alone as it is in dogs with simultaneous ligation of the aorta and portal vein, i. e., four hours and thirty-two minutes and four hours and eighteen minutes, respectively. The duration of life of cats with simultaneous ligation of the aorta and portal vein was fifty minutes shorter than the duration of life in cats with ligation of the aorta alone. Tracings of blood pressure taken on several dogs for at least an hour after simultaneous ligation of the aorta and portal vein failed to reveal a semblance of the drop which invariably follows ligation of the portal vein alone (chart 3). If the shock of ligation of the portal vein was due to toxic factors originating in the splanchnic area the animals should die practically as soon after simultaneous ligation of the aorta and portal vein as after ligation of the portal vein alone. That they lived several hours longer is obviously due to the fact that ligation of the aorta prevents the accumulation of blood in the portal system behind the ligature and thus prevents its consequent loss to the general circulation.
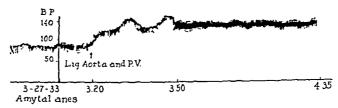
Chart 3.—Blood pressure tracing obtained after the simultaneous ligation of the aorta and the portal vein, showing the absence of a drop which accompanies ligation of the portal vein alone (chart 1). The increased pressure is characteristic of ligation of the aorta.

Lest it be suggested that the presence of blood under pressure in the portal system is a factor in the possible production of a toxin, we conducted some experiments in which, in addition to ligation of the aorta and portal vein, we injected several hundred cubic centimeters of blood into the superior mesenteric artery. This produced the same type of engorgement and cyanosis of the intestines as is seen following portal ligation alone. Thus into the superior mesenteric artery of one dog weighing 6 Kg. we injected 570 cc. of blood, beginning a few minutes after simultaneous ligation of the aorta and portal vein. We repeated the experiment in another dog weighing 6 Kg., injecting 400 cc. of blood into the superior mesenteric artery. The blood pressure was observed for eighty and eighty-five minutes, respectively. There was a sharp rise in the blood pressure at the time the aorta was tied (chart 4), but in neither case did there occur the fall of blood pressure which is characteristic of ligation of the portal vein alone.

Ransohoff [13] demonstrated that simple pressure on the portal vein in animals as well as in human beings produces a sharp and almost immediate fall in blood pressure which, if continued, would probably lead to shock similar to that following actual ligation of the portal vein. This also supports the idea that the effect is due primarily to a loss of blood into the tissues drained by the portal vein.

13. Ransohoff, J. L.: Cause of Sudden Fall in Blood Pressure While Exploring the Common Bile Duct, Ann. Surg. **48**:550, 1908.

He noted the same drop in blood pressure whether the finger was inserted into the foramen of Winslow or a clamp was applied to the portal vein.

7. *Removal of Intestinal Tract.*—After ligation of the portal vein an attempt was made in a few dogs to prolong life by ligation of all vessels and resection of the entire gastro-intestinal tract including the spleen. This can be done in the dog very rapidly. We noted that while this would prevent the usual death, like transfusion of blood, it had to be done before the animal passed into the irremediable stage. On the other hand, even when life was prolonged, the blood pressure remained low and never regained its normal level (chart 5). One of the factors which prevents the blood pressure from regaining its normal level in this experiment may be that the intestinal tract acts as a source of fluid in replenishing the volume of blood after a hemorrhage.
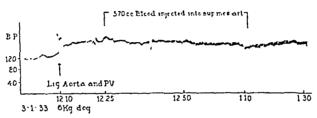
Chart 4.—Blood pressure tracing obtained after simultaneous ligation of the aorta and the portal vein. To imitate the intestinal engorgement characteristic of portal ligation alone, 570 cc. of blood from another dog was injected into the splanchnic area through the superior mesenteric artery. No change in the curve or in the behavior of the animal was observed (compare with chart 3).
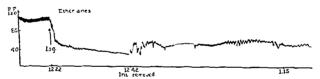
Chart 5.—Blood pressure tracing showing the characteristic fall after ligation (*Lig.*) of the portal vein. Twenty minutes later the entire splanchnic area was resected, with a prompt improvement of blood pressure and prolongation of life, but without regaining the normal level.

COMMENT AND SUMMARY

It seems clear that the rapid death which so regularly follows total and complete occlusion of the portal vein is due to circulatory failure, because of extensive loss of blood from the general circulation into the trapped splanchnic area. No evidence of the production or absorption of a toxic substance (by guinea-pigs and white mice) was found. On the other hand the evidence in favor of the purely physical factor was uniform and consistent, and was obtained from a variety of experiments which, previously described in detail, may be summarized briefly. The increase in weight of the splanchnic area following occlusion of the portal vein was great enough, on the basis of the amount of entrapped

blood it contained, to have caused death from shock alone, since the lost blood was sufficient to lower the systemic blood pressure below that compatible with life. The fall in blood pressure was measured in many animals and was similar to that noted after an extensive hemorrhage except that the pressure was sustained at a low level until death. Moreover, the behavior and appearance of the animal after ligation of the portal vein were similar to those seen after marked loss of blood from hemorrhage. Attempts to raise the blood pressure and prolong life by transfusions of blood were successful, and it was possible to postpone death for over six hours. At this time gangrenous changes in the intestines began to introduce another factor. Finally, it was possible to prolong life and prevent the characteristic fall of blood pressure ordinarily following occlusion of the portal vein by ligating the aorta above the celiac axis, which effectively stopped blood from entering the splanchnic area. These animals lived only a few hours, but they lived as long as animals with ligation of the aorta alone. Moreover, the results of the experiment were the same if in addition several hundred cubic centimeters of blood were injected into the mesenteric arteries to produce the cyanosis and congestion ordinarily seen after ligation of the portal vein.

√ Death following ligation of the portal vein, while undoubtedly due to the same mechanism as shock from hemorrhage, is probably hastened by the fact that ligation at the same time prevents the gastro-intestinal tract from aiding in the loss of fluid. It is probable that ordinarily much of the fluid which rushes into the circulation to maintain blood volume after a serious hemorrhage comes from the intestinal tract, from which it can most easily be spared. While such a conception rests on a number of clinical observations, its final proof awaits further study.

Another interesting mechanism noted in our experiments was the irremediable changes which occur when a low blood pressure is maintained too long. What this level is probably differs with the individual, but if this critical level is not raised soon enough it can never be corrected, no matter how much blood is transfused. This fact was noted during the World War, when it was found that massive transfusions as well as other means failed to save a soldier who had been in shock for too long a time. The effect may be due to changes produced in the nerve cells. It is likely that too low a pressure slows the metabolic exchange and causes irreparable alteration in the central nervous system. It is known that complete cessation of cerebral circulation for even six minutes may permanently destroy the power of nerve tissue to function even though one can demonstrate no morphologic alteration in the cells. On the other hand, the defect caused by a very low blood pressure may be due to increased capillary permeability. It is obvious that no amount

of blood will succeed in raising the pressure if it leaves the vascular system as fast as it is poured in. The matter merits further experimental study.

CONCLUSIONS

The rapid death which occurs after total and complete ligation of the portal vein is not due to the effect of a toxin elaborated by the gastro-intestinal tract. It is to be explained on the basis of a loss of blood from the systemic into the portal system of a sufficient magnitude to reduce blood pressure below that compatible with life.

FIFTY-THIRD REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

JOHN G. KUHNS, M.D.

EDWIN F. CAVE, M.D.

SUMNER M. ROBERTS, M.D.
AND
JOSEPH S. BARR, M.D.
BOSTON

JOSEPH A. FREIBERG, M.D.
CINCINNATI

JOSEPH E. MILGRAM, M.D.
NEW YORK

ROBERT I. STIRLING, F.R.C.S. (EDIN.)
EDINBURGH, SCOTLAND
AND
PHILIP D. WILSON, M.D.
Advisory Editor
BOSTON

CONGENITAL AND DEVELOPMENTAL DEFORMITIES

End-Results Following Bloodless Reduction of Congenital Dislocation of the Hip.—Becker [1] reported the end-results in 97 congenital dislocations of the hip in 67 cases from the Erlangen University Clinic, all reduced by von Kryger by the Lorenz method. Following reduction, the hips were kept in plaster casts in the first Lorenz position for six months. This was followed in some instances by rest in bed and by physical therapy. The cases were divided into three groups: (1) those in which reduction was performed over twenty years before the study was made; (2) those in which it was performed ten or more years before, and (3) those in which it was performed over five years before. In the first group there were 36 dislocated hips. Five of these had remained reduced; 4 showed slight subluxation, 12 severe subluxation and 15 redislocation. Of the 4 hips with mild subluxation, 2 showed mild coxa vara and 2 severe coxa vara with marked arthritis deformans, although there was excellent socket formation. Over half of the 12 hips which showed severe subluxation and 13 of the 15 which showed redislocation were painful, the pain usually appearing first in the third

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This Report of Progress is based on a review of 203 articles selected from 337 titles appearing in medical literature approximately between July 1, 1933, and Oct. 28, 1933. Only those which seemed to represent progress have been selected for review.

1. Becker, F.: Deutsche Ztschr. f. Chir. **241**:273, 1933.

decade. All of the reductions with permanent results had been done before the patient was 3½ years of age. There were 19 hips in the second group. Four had remained reduced; 5 showed slight subluxation, 5 severe subluxation and 5 redislocation. The third group consisted of 34 dislocated hips. Five had remained reduced; 15 showed slight subluxation, 7 severe subluxation and 7 redislocation. The femoral head and socket of the hips in which redislocation and severe subluxation occurred were markedly altered. A flat femoral head, anteversion, coxa vara and slipping of the upper femoral epiphysis were observed exactly as in adolescent coxa vara. The femoral head and that half of the pelvis tended to be smaller than on the normal side. In 9 cases there was severe arthritis deformans. It appeared to make no difference so far as function and pain were concerned whether the head made a new socket or hung loosely in the soft tissues. Increasing subluxation or spontaneous healing was apparently uninfluenced by treatment. Early plastic surgical repair of the acetabular roof was suggested as a possible procedure in some of these cases. Only hips in which reduction was proved roentgenologically and clinically offered a good prognosis for the future.

[Ed. Note.—These end-results are much poorer than those found in many American clinics. Clinical and pathologic studies have taught us that early reduction performed with the minimum of trauma and early, guarded weight-bearing supplemented by physical therapy offer most in these cases.]

Subluxation of the Hip Joint Secondary to Maldevelopment of the Acetabulum.—Simons [2] studied a number of cases of subluxation of the hip joint caused by faulty acetabular development, called by Klapp, "coxa valga luxans." One or both sides of the acetabulum might be affected. In roentgenograms the acetabulum appeared flat and ellipsoid, often without an edge to the acetabular roof. The outer margin of the femoral head was wider than the medial margin, apparently conforming to the shape of the acetabulum. These cases could be differentiated from coxa plana by the character of the upper femoral epiphysis, and were seen chiefly in females. In all of the cases studied arthritis deformans developed later in life.

Congenital Torticollis.—Fitzsimmons [3] discussed the etiology of congenital torticollis. At birth the venous supply of the sternocleidomastoid muscle was obstructed, and fibrosis resulted similar to that seen in the muscles of the forearm in Volkmann's ischemic contracture. The author thought that the ischemia was the result of the temporary venous obstruction, rendered permanent by patchy intravascular clotting.

2. Simons, B.: Beitr. z. klin. Chir. **157**:505, 1933.
3. Fitzsimmons, H. J.: New England J. Med. **209**:66 (July 13) 1933.

Idiopathic Osteopsathyrosis.—Goin [4] presented a review of the literature on osteopsathyrosis and osteogenesis imperfecta and suggested that the two conditions might be separate diseases or that they might represent different phases of the same disease. The disease occurred in infancy and in childhood and was characterized by a deficiency in the number and function of osteoblasts. There were the hereditary and nonhereditary forms, the former being characterized by blue sclerae. In both, multiple fractures were frequent, which healed rapidly but with deformity. Fractures were rare after puberty, at which time the disease usually subsided. Nothing was known as to the cause or the method of treatment of the disease, but the clinical and roentgenographic findings were characteristic.

TUBERCULOSIS

Tuberculosis in Infancy and in Childhood.—Katzeff [5] made a statistical study of the cases of tuberculosis seen at the Children's Hospital in Boston during a forty-six year period (from 1884 to 1930). The incidence of orthopedic forms of tuberculosis showed a high level during this period and a steady decrease in 1924, with a marked decrease from 1925 to 1930. The lowest point, 22.2 per cent of the total number of cases, was reached in 1930. Just the opposite was true of the nonorthopedic forms of tuberculosis. The incidence rose, until in 1930 a peak of 17.7 per cent was reached. This study confirmed the clinical impression that tuberculosis of the osseous system was a disappearing disease, and that this form of tuberculosis responded more favorably to the measures of preventive medicine than the nonorthopedic forms.

Tuberculosis of the Greater Trochanter.—Meyerding and Mroz [6] reported 19 cases of tuberculosis of the greater trochanter and of the trochanteric bursa. Diagnosis in all the cases was proved. The disease was most prevalent in the first and second decades of life. In 16 of 19 cases, tuberculosis elsewhere in the body (lungs, joints and genitourinary tract) was demonstrated. In only 2 cases was the bursa alone involved. Cure was obtained in both cases by extirpation of the bursa. When the trochanter was involved, radical excision of the infected area was done. Persistent sinuses formed in 4 of the cases. Without treatment, the infection might spread to the neck of the femur and the hip joint.

Tuberculosis of the Diaphysis.—Brower and Downs [7] reported several cases of tuberculous involvement of the diaphysis of the long bones.

4. Goin, L. S.: Am. J. Cancer **17**:668, 1933.

5. Katzeff, M. G.: New England J. Med. **209**:83 (July 13) 1933.

6. Meyerding, H. W., and Mroz, R. J.: Tuberculosis of the Greater Trochanter, J. A. M. A. **101**:1308 (Oct. 21) 1933.

7. Brower, R. S., and Downs, E. E.: Am. J. Roentgenol. **29**:617, 1933.

In 1 case the lesion was confined entirely to the diaphysis of the fibula. An extensive discussion of the etiology was given, including a résumé of the literature. Diagnosis of these lesions was difficult, and as they were rare, the diagnosis was easily missed.

Multiple Tuberculous Spondylitis.—Thrap-Meyer [8] reported the finding of multiple tuberculous spondylitis in 7 patients suffering from pulmonary tuberculosis. In 6 patients there were 2 tuberculous foci in the spine with normal vertebrae between, and in 1 patient there were 3 foci. The author believed that the spinal involvement was of hematogenous origin. He·felt that contact with tuberculous abscesses must be considered as a means of spreading the infection to the spine, but he believed this to be rare. In these cases there were no symptoms of irritation of the spinal cord. In all, the symptoms were localized wholly to the caudal focus.

Technic and Dosage of Heliotherapy in Surgical Tuberculosis.—Rollier [9] was of the opinion that heliotherapy to be efficacious should always be strongly individualized. It should be adapted to the season and climate and to the state of the subject's resistance. He enumerated some general rules, however. General heliotherapy should always be carried out, no matter how localized the manifestation of tuberculosis appears to be. Heliotherapy should be given in graduated doses, commencing in all cases with treatment of the extremities; usually three exposures of three minutes each with ten minute rest periods are given. In most cases, after the eighth day exposures can be given with intervals of ten minutes between the periods—for from one to one and one-half hours for the extremities, from three-quarters to one hour for the abdomen, from one-half to three-quarters hour for the thorax and one-quarter hour for the neck. Longer periods of exposure can be given when the skin is well pigmented. Insolation that is interrupted by periods of rest exercises a more tonic and vitalizing action than when it is continuous.

OSTEOMYELITIS

Acute Infectious Osteomyelitis.—From the examination of 262 consecutive cases of acute infectious osteomyelitis, Pyrah and Pain [10] came to the conclusion that moderately conservative treatment was the best for this condition. In the case of average severity they advocated an incision of the periosteum, extending up to the epiphyseal cartilage. Only when frank pus was found by drilling the metaphysis should any opening of the bone be carried out. Compact bone should be removed to uncover the pus, but no further procedure should be used except to

8. Thrap-Meyer, H.: Norsk mag. f. lægevidensk. **94**:641 (June) 1933.
9. Rollier, A.: Brit. J. Phys. Med. **7**:235, 1933.
10. Pyrah, L. N., and Pain, A. B.: Brit. J. Surg. **20**:590, 1933.

provide for drainage and irrigation. If the patient was very ill, or the infection very acute, they felt that treatment should include periosteal incision. In this series of cases there was a mortality of 27.1 per cent.

Osteomyelitis in Ischiopubic Synchondritis.—Haberler [11] reported 3 cases of this condition in children, 2, 6½ and 8 years of age. The disease began with fever, which subsided with rest. The symptoms were those of inflammation of the hip joint, with localized tenderness at the ischiopubic junction. In 1 case a sequestrum formed; in 1 there was complete healing, and in the other there was sclerosis of the bone. Conservative therapy was followed by complete functional recovery. A review of the literature of this rare type of osteomyelitis was given.

FUNGOUS INFECTION OF BONE

Actinomycosis of the Spine.—A case of actinomycosis of the bone was reported by Tabb and Tucker [12] in which the etiology was proved by the recovery of Actinomyces from a draining cervical spine and from the sputum. The spinal lesion was characterized by discrete punched-out areas in the bodies of the tenth and eleventh dorsal vertebrae, without collapse of the vertebral bodies. Large paravertebral masses were seen in the roentgenograms. Pulmonary infection with actinomycosis existed. In spite of the area of the spine involved, there was much less pain than would usually be found with a similar tuberculous lesion.

Blastomycosis of the Bone.—Sixteen cases of blastomycotic infection of the bone were reported by Warding and Blair.[13] The importance of early recognition of the disease by laboratory examination of the exudate was stressed. Osseous lesions, while showing extensive roentgenologic changes, were associated with little fever, with no elevation in the number of white blood cells and with a slowly progressive involvement. In the absence of pulmonary lesions or multiple systemic lesions, cures were observed following therapy with potassium iodide.

[Ed. Note.—There have been numerous cases of blastomycosis reported, but it is probable that many are overlooked, especially in the early stages of the disease. The 16 cases reported by Tabb and Tucker were found in a thinly populated semirural community.]

POLIOMYELITIS

Acute Poliomyelitis as a Primary Disease of the Central Nervous System.—In a study of acute poliomyelitis, Faber [14] concluded that the clinical course of the disease corresponded with the progress of the infec-

11. Haberler, G.: Arch. f. klin. Chir. **175**:625, 1933.
12. Tabb, J. L., and Tucker, J. T.: Am. J. Roentgenol. **29**:628, 1933.
13. Warding, D. B., and Blair, C. C.: South. M. J. **26**:315, 1933.
14. Faber, H. K.: Medicine **12**:83, 1933.

tion through and within the central nervous system, the portal of entry being the olfactory mucosa. The virus spread by extension from the olfactory bulb through the olfactory tracts to the interbrain (the hypothalamus and thalamus), thence through the spinothalamic tract to the posterior horns and intervertebral ganglions of the cord, where it produced the later preparalytic symptoms, and thence to the anterior spinal horns. In discussing the therapy, the author felt that serum, and especially tested human serum, should be administered intravenously in large doses. Considering the early infiltration of the involved areas of the cord, the author believed that by intrathecal injection of serum the immune antibodies reached the infected areas in insufficient concentration. It was by the intravenous injection of large amounts of tested serum that results might be obtained. With the present knowledge of the disease, the author did not feel justified in discarding the use of serum of known antibody potency.

[ED. NOTE.—This article of more than 100 pages cannot be discussed adequately in a brief abstract. It merits careful reading for those interested in acute poliomyelitis. The final word has not yet been said in regard to serums in the early treatment of poliomyelitis.]

Treatment of Acute Poliomyelitis with Transfusions of Convalescent Blood.—Sherman [15] treated 71 patients suffering from poliomyelitis with transfusions of whole blood from donors convalescing from poliomyelitis. From 150 to 400 cc. of blood was given intravenously. Thirty-five patients were in the preparalytic stage, while 36 were paralyzed. There were 5 deaths; 2 of the patients were moribund when the transfusion was given. Paralysis developed in only 3 of those treated in the preparalytic stage. In some of the cases transfusion seemed to be beneficial in shortening the period of fever and the duration of other symptoms of the disease. The author advocated the registration of persons who had recovered from poliomyelitis for use as donors in epidemics.

CHRONIC ARTHRITIS

Rheumatic Conditions of the Tendon and Muscle Attachments.— Under the term "tendinitis," Kahlmeter [16] described a condition of tenderness, swelling and pain of the muscle or of its tendinous attachments, not implying thereby that true inflammatory changes were present. The general form, "polytendinitis," was shown to resemble acute rheumatic polyarthritis closely, and the local form to include such conditions as tennis elbow and calcaneal spur. Especial attention was drawn to tenderness of the quadriceps tendon at the upper border of the

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15. Sherman, T.: Deutsche med. Wchnschr. **59**:1332, 1933.
16. Kahlmeter, G.: Lancet **1**:1338 (June 24) 1933.

patella. The author had 25 patients with this condition. They experienced pain on walking which radiated up the front of the thigh, but there was no swelling of the knee joint or any tenderness except in the localized area above the patella. Cure was obtained in all cases of "tendinitis" by roentgen treatment. Unfortunately, no indication was given as to the appropiate dosage.

Economics of Rheumatism.—From the government report of 1924, Buckley [17] deduced that "rheumatism" accounted for one sixth of the industrial invalidism in England and concluded that the loss of wages and disbursements by approved societies for sickness, etc., amounted to more than 20,000,000 pounds for the year. He was of the opinion that the problem was so extensive that voluntary hospitals could not cope with it, and cited the methods of financing more elaborate schemes which were in operation in many countries and included, when necessary, reeducation for new employment.

Transitory Arthritis of the Hip Joint in Childhood.—The necessity for early and exact diagnosis of arthritis of the hip in children was emphasized by Butler,[18] who gave a report of an investigation in 97 cases. Of these, 56 were proved to be tuberculous and 34 to be of a transitory nature, with no abnormality shown by roentgenographic examination. Seven occurred as reactions to localized infection of the bones near the joints. All persons with questionable arthritis of the hips were admitted to the hospital to be observed, and were treated by rest, extension or fixation according to their individual requirements. The transitory type of arthritis cleared up excellently, and its chief importance lay in the fact that clinically it so closely resembled an early tuberculous infection. In the vast majority of the cases an entirely negative roentgen picture could be taken to exclude a tuberculous infection.

SCOLIOSIS

Mechanics of Scoliosis.—Rogers [19] reviewed the various theories of the mechanics of scoliosis and showed that none of them was adequate to explain the entire mechanical evolution of scoliosis. He grouped the muscles acting on the spinal column into flexor, extensor, deep torsion and transverse traction muscles. It was found that a unilateral relaxation of the extensor group of muscles could produce the three elements of deformity in scoliosis; lateral deviation, rotation and kyphosis. The author believed that hyperextension was the best mechanical position in which to treat scoliotic deformities.

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17. Buckley, C. W.:   J. State Med. **41**:282, 1933.
18. Butler, R. W.:   Brit. M. J. **1**:951 (June 3) 1933.
19. Rogers, S. P.:   Mechanics of Scoliosis, Arch. Surg. **26**:962 (June) 1933.

THE SPINE

Changes in the Articulations of the Vertebral Processes, a Little Considered Cause of Backache.—Lange[20] called attention to changes in the articulations of the vertebral processes as found in various disabilities. Special technic was necessary to demonstrate these changes in the roentgenograms: for the cervical vertebrae, the articulations were best shown in lateral views with the neck in full extension; for the dorsal spine, the roentgenograms were taken from the side with the patient turned from 15 to 20 degrees from the true lateral position with the scapula rotated outward; for the lumbar spine, the articulations were shown in anteroposterior views and in views taken at a deviation of 45 degrees from the true lateral position. The changes commonly found in conditions such as scoliosis, vertebral fractures and postural changes in stout persons were first a loss of the parallel form of the surface of the joints followed by arthritic changes. The author discussed the possible relationship of these changes to pain and to limitation of motion in the spine.

Backache from Relaxation of the Sacro-Iliac Joint.—Bragard,[21] in Lange's Clinic in Munich, reviewed over 100 cases of backache caused by relaxation of the sacro-iliac joint. He attempted to explain on an anatomic background the symptomatology and the reactions to the various diagnostic tests. Pain, he believed, was due to a tearing of the articular capsule and to overstretching of the surrounding ligaments and muscles; later there appeared degeneration of the articular cartilage, periostitis and arthritic changes. Roentgenograms helped very little in diagnosis. Treatment in the acute cases consisted of circular adhesive strapping from the trochanters to the navel. This strapping was renewed if pain was still acute. A pelvic band or corset was next used. Heat or diathermy and massage were given, and later gymnastics were advocated, first with passive, and later with active, motion. Operations for the relief of symptoms, such as are described in the American literature, were not required in any of these cases.

TUMORS

Bone Endothelioma and Primary Epithelial Bone Tumors.—Petrow and Glasunow[22] collected 7 cases of primary epithelial tumor of the long bones from the literature and added a case of their own. They concluded that a number of the endotheliomas of the bone reported in the past were metastatic epithelial tumors; others were probably caused by metastases, and still others were of unknown origin. Epithelial

20. Lange, M.: München. med. Wchnschr. **80**:1134 (July 21) 1933.
21. Bragard, K.: München. med. Wchnschr. **80**:1240 (Aug. 11) 1933.
22. Petrow, N., and Glasunow, M.: Arch. f. klin. Chir. **175**:589, 1933.

tumors must be included in primary tumors of the bone. Their origin was probably in embryonic ectodermal inclusions. These tumors almost always involved the tibia. Histologically, they were similar to basal cell carcinoma. It was not definitely known whether or not they were malignant.

Primary Echinococcosis of Vertebra.—Pessano [23] reported 2 cases of hydatid cyst of the vertebra, one in a 26 year old man with a lesion between the eighth and the twelfth dorsal vertebra and the other in a 14 year old girl. The diagnosis was made only after exploratory operation, the usual diagnosis before operation being tuberculous spondylitis. Compression of the spinal column was common. Often no symptoms were present until trauma to the spine occurred. Surgical intervention with evacuation and destruction of the cysts was the treatment of choice. Arsenical preparations were an aid in treatment. The cysts were always multilocular and were found in the spongy or areolar tissue of the vertebral body. A complete review of the literature was given.

CIRCULATORY DISTURBANCES OF THE EXTREMITIES

Study of the Dorsalis Pedis and Posterior Tibial Pulses in One Thousand Persons Without Symptoms of Circulatory Conditions of the Extremities.—Morrison [24] studied the pulse in the posterior tibial and dorsalis pedis arteries in 1,000 persons who had no symptoms of any circulatory disturbance in the extremities. Absence of the pulse in one or more of the vessels was noted in 191 persons. All pulsations were absent in 19. Absence of pulsation was more common in the posterior tibial than in the dorsalis pedis arteries. The patients with absent pulsation were of all ages. The author stated that absence of pulsation did not necessarily mean disease of the arteries.

Evaluation of Various Methods of Investigating the Circulation in the Lower Extremities.—Kramer [25] attempted to evaluate the various methods of investigation of the circulation in the lower extremities by considering the oscillometer, injections of histamine, heat, measurements, intradermal injections of salt solution, roentgenograms, roentgenographic visualization of the vessels and the sphygmotonograph. In many instances the author found that a careful history and physical examination did not give adequate data in regard to the circulation. The conclusions drawn were that all of these methods had merit. The oscillometer gave evidence of circulation in deep vessels which could not be palpated. Injections of histamine were of value, particularly for the study of the superficial circulation. Roentgen studies were of little

23. Pessano, J. E.: Semana méd. **1**:2126 (June 29) 1933.
24. Morrison, H.: New England J. Med. **208**:438 (Feb. 23) 1933.
25. Kramer, D. W.: Am. J. M. Sc. **185**:402, 1933.

value, except in rare instances, particularly in cases of diabetes. The calorimetric methods were chiefly of value in differentiating between vasospastic and occlusive lesions of the vessels.

RUPTURES OF MUSCLES AND TENDONS

Spontaneous Rupture of the Long Tendon of the Biceps.—Oppolzer [26] was able to collect over 200 cases of rupture of the long tendon of the biceps brachialis muscle. It was found most commonly in muscular persons and particularly on the left side in glass blowers. In less muscular men, it was seen only after the age of 45. In the author's own cases the classic signs were absent. These were known as Heuter's sign (pain in the shoulder when the supinated forearm was flexed), Pagenstecher's sign (subluxation of the humeral head upward and inward) and Cruveilhier's sign (elevation of the humeral head). Conservative treatment was advised for persons too old to perform heavy work. The author sutured the peripheral portion of the tendon beneath the tendon of the pectoralis major muscle to the pectoralis attachment on the humerus. Various authors had estimated the disability from this injury to be from 10 to 50 per cent.

Separation of the Symphysis Pubis.—Boland [27] reported 10 cases of separation of the symphysis pubis occurring during delivery. He found the ratio to be 1 in 685 deliveries. He believed that this lesion was due to trauma resulting from the descent of the fetal head associated with an inherent weakness of the ligaments about the symphysis. Associated with the separation of the symphysis pubis was involvement of the sacro-iliac joints and posterior displacement of the acetabula. The onset of the symptoms was usually acute with pain over the symphysis and in the lower part of the back. The onset of symptoms varied from two months before delivery to twelve days after delivery. On physical examination there was often a separation of the symphysis pubis of from one to two fingerbreadths; a waddling gait was frequently observed, and tenderness was present over the sacro-iliac joints. Treatment consisted in placing the patient on a hard bed and in circular strapping of the pelvis with adhesive plaster. If one pubis was elevated in the roentgenograms, traction was applied to the leg on that side until the pubes were level. When there was wide separation, a canvas hammock with overhead traction on the sides was used. For later convalescence, a butterfly type of brace was applied. This separation appearing in pregnancy was no indication for immediate delivery. It was treated as a complication, and delivery was allowed to proceed to term. The separation was found to recur in each succeeding pregnancy.

26. Oppolzer, R.: Deutsche Ztschr. f. Chir. **241**:281, 1933.
27. Boland, B. F.: New England J. Med. **208**:431 (Feb. 23) 1933.

Injuries of the Semilunar Cartilage.—Wright [28] reported on the conservative treatment of a group of patients with primary or recurrent dislocation of the internal semilunar cartilage. They were treated by the following definite routine: 1. The displaced cartilage was reduced by manipulation, preferably with the patient under the influence of an anesthetic. 2. From 5 to 10 minims (0.3 to 0.6 cc.) of tincture of iodine was injected at the point of greatest tenderness. The author felt that this stimulated the feeble reparative process of the cartilage. 3. Fixation of the leg in full extension in a light plaster cast was carried out. 4. Walking was encouraged in the cast after two days. 5. Faradic stimulation was used to aid in the redevelopment of the weakened quadriceps muscle. 6. The inner border of the heel was raised to remove the strain from the knee. Five primary and 28 recurrent dislocations were treated in this manner. One patient failed to improve, and the cartilage was removed by operation. Two patients failed to report for follow-up examination. The rest showed excellent results. There were no recurrences of the dislocation.

Adaptation to New Function by Muscles Shifted in the Course of Tendon Transplantation.—Lange,[29] after many years of experience in the transplantation of tendons, concluded that muscles shifted in their course adapted themselves to new functions only after long and careful training. His procedure had been to leave the limb in a plaster cast for six weeks. Occasionally, electrical stimulation of the transplanted muscle was begun in the fifth week. After the cast was taken off, the limb was placed in a apparatus which moved the affected joint by millimeter gradations. By such methods the intelligent patient learned to use the transplanted muscle in from a few weeks to several months. The author reported the use of silk tendons for various types of muscle transplantation.

The Possibility of Recording Noises Produced in Joints.—Erb,[30] by the use of an oscillograph, was able to record the noises produced in knee joints and to analyze to some degree their frequency and significance. Not only were the noises recorded that are usually heard but also others the character of which had not yet been studied.

Bony Nucleus of the Anterior Inferior Iliac Spine.—Janker [31] observed 2 cases in which the anterior inferior iliac spine had not fused on one side at the age of 18 and on both sides at the age of 20. Anatomists have taught that the nucleus of this process appears at the age

28. Wright, C. S.: Canad. M. A. J. **28**:618 (June) 1933.
29. Lange, F.: München. med. Wchnschr. **80**:1133 (July 21) 1933.
30. Erb, K. H.: Deutsche Ztschr. f. Chir. **241**:236, 1933.
31. Janker, R.: Deutsche Ztschr. f. Chir. **241**:477, 1933.

of 15 or 16 and fuses within a year. Such osseous nuclei not fused to the ileum might be confused with avulsions when injury has occurred in this region.

ORTHOPEDIC OPERATIONS

Treatment of Athetosis and Dystonia by Section of the Extrapyramidal Motor Tracts.—Putnam [32] sectioned the extrapyramidal motor tracts in 5 cases of athetosis and dystonia. In 4 of the cases there was definite improvement as far as the uncontrolled muscular activity was concerned. There were no permanent ill effects from the operation. The operation in each case was described, and the histories were presented.

Treatment of Injuries of the Semilunar Cartilage.—Stefanini [33] reviewed the various incisions used in operating on semilunar cartilage. He objected to most of them because they did not allow sufficient exposure for the total removal of the cartilage. Failure to remove the posterior part of an injured cartilage sometimes resulted in recurrence of symptoms, necessitating a second operation. The author preferred an enlargement of Baker's incision, making a J with the long arm parallel to the patella and then turning the incision outward as far as the lateral ligament.

[ED. NOTE.—Just how this incision gives better exposure to the posterior portion of the cartilage than the incision of Timbrel Fisher is difficult to see. The noteworthy point, however, seems to us to be that it is important to remove the whole cartilage and to use an incision that allows access to the posterior rim of the cartilage.]

Countersinking the Astragalus.—Brewster [34] described an operation which he has performed for the last six years on paralyzed feet. This consisted of countersinking the previously prepared astragalus into a rectangular well in the os calcis. This procedure enabled the operator to set the foot well back, to lower the tibioastragalar joint so that dorsal and plantar flexion were limited, and to gain lateral stability by fusion of the calcaneo-astragaloid joint.

[ED. NOTE.—This operation seems to offer the advantages of an astragalectomy without the operative difficulty and without the resulting mutilation.]

Tendon Transplantation in the Lower Extremity.—Ober [35] discussed the general considerations of tendon transplantation. In the cases selected for operation, he said, all the tendons must have sufficient power

32. Putnam, T. J.: Treatment of Athetosis and Dystonia by Section of Extrapyramidal Motor Tracts, Arch. Neurol. & Psychiat. **29**:504 (March) 1933.
33. Stefanini, J.: Rev. de chir., Paris **52**:349, 1933.
34. Brewster, A. H.: New England J. Med. **209**:71 (July 13) 1933.
35. Ober, F. R.: New England J. Med. **209**:52 (July 13) 1933.

so that when one is transplanted the others will continue to stabilize the joint. Deformities must be corrected (as by stabilizing operations) before transplantation is done. The tendon selected for transplantation should have power enough to balance its opponent. Adhesions must be prevented, and the question of leverage must be considered. The tendon should be inserted preferably into bone. The transplanted tendon should parallel as nearly as possible the course of the paralyzed one. As a general rule, the transplant should be under enough tension to hold the foot in a corrected position. Various tendon transplantations about the ankle, knee and hip joints were discussed in detail and the operative technic was described.

Resection of the Shoulder Joint in Tuberculosis.—Richard and Courvoisier [36] stated that surgical treatment of the upper extremity was the opposite of treatment of the lower extremity. In the lower extremity fusion was desired, but in the upper extremity, motion. They considered that fusion of the shoulder joint was being done too frequently, and that resection was preferable when possible. Conditions essential to resection were: (1) good musculature about the shoulder, with recognition of the fact that some atrophy is invariably present, and (2) intact nerves. Contraindications were: (1) very active lesions with multiple open sinuses, resection in these cases resulting in ankylosis, and (2) old quiescent lesions that had caused ankylosis and resulted in extreme muscular atrophy. Except for these contraindications, the joint of the shoulder was always amenable to resection. The presence of an abscess or a sinus was not a contraindication. Through an anterior incision the muscular attachments at the tuberosities were separated; subsequently the humeral head was removed at the surgical neck except in children in whom the epiphysis was left intact. The articular cartilage was then curetted from the glenoid. Particular care was taken to preserve the deltoid muscle and its nerve supply. From two to five weeks of mobilization followed. Cases illustrating both good and bad results were described.

FRACTURES AND DISLOCATIONS

Avulsions of the Carpal Bones.—Ernst and Römmelt [37] called attention to avulsions of small portions of the periosteum and bone from the carpal bones. Ninety personal observations were recorded. In his own material of 6,000 wrists the roentgenograms showed no definite accessory bones. Lesions of the semilunar and large multiangular bones were most commonly found to cause pain. The other bones healed in

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36. Richard, A., and Courvoisier, J. N.: Presse méd. **41**:290 (Feb. 22) 1933.
37. Ernst, M., and Römmelt, W.: Deutsche Ztschr. f. Chir. **241**:438, 1933.

a few days. Traces of such injury could be demonstrated in the roentgenograms for long periods.

Mechanics of Supracondylar Fracture of the Humerus.—Coenen [38] divided supracondylar fractures according to the mechanism causing the fracture into flexion and extension fractures. In a group of 38 supracondylar fractures, 29 were flexion fractures and 9 extension fractures. The flexion type of fracture was caused by a fall on the forearm portion of the acutely flexed elbow. The fracture line was higher on the posterior aspect of the humerus than on the anterior aspect. The extension type of fracture resulted from a fall or blow on the upper arm portion of the elbow. This caused the fracture line to be higher on the anterior aspect of the humerus than on the posterior aspect. Reduction of the flexion type was secured by traction on the forearm forward and distally, with acute flexion of the elbow. Reduction of the extension type of fracture was more difficult, and skeletal traction through the olecranon was sometimes required.

Fractures and Dislocations in the Region of the Elbow.—Wilson [30] made a study of 176 cases of injury about the elbow all of which had been followed for at least a year. Each type of injury was discussed from the point of view of treatment and prognosis, and attention was called to the various complications and dangers that should be avoided. Conclusions drawn from the whole groups were that proper treatment which commenced early obtained better end-results than are commonly supposed to occur in such injuries.

[ED. NOTE.—This paper is a detailed exposition on the treatment of injuries about the elbow. It represents part of a seven years' study of 4,536 bony injuries treated in the service for fractures of the Massachusetts General Hospital.]

Ununited Fractures of the Shaft of the Humerus.—Owen [40] considered ununited fractures of the humeral shaft to be those in which there was no evidence of union six months after injury. At the time stimulation of union was difficult, and half-way measures were unavailing. He advised an autogenous bone graft followed by fixation for four months. Foreign materials were avoided, as it was considered that in spite of firm fixation they often hindered union. In 7 of the 8 cases reported the results were successful.

[ED. NOTE.—The experience of the editors is in entire accord with these findings.]

38. Coenen, H.: München. med. Wchnschr. **80**:1174 (July 28) 1933.

39. Wilson, P. D.: Surg., Gynec. & Obst. **56**:335, 1933

40. Owen, W. B.: Ununited Fractures of the Shaft of the Humerus, J. A. M. A. **101**:569 (Aug. 19) 1933.

Recognition of Fractures of the Laminae of Vertebrae in the Roentgenogram.—Von Oettingen [41] called attention to the difficulty of recognizing fractures of the laminae of vertebrae, particularly late after injury. He urged careful examination of early roentgenograms with this lesion in mind. Fractures extending through the pedicles into the transverse processes might be difficult to recognize after healing has occurred, save for the residual broadening of the transverse processes.

Intra-Articular Fractures of the Proximal End of the Tibia.—Mikkelsen [42] reviewed 248 cases of intra-articular fractures of the proximal end of the tibia—160 from the Kommune Hospital in Copenhagen and 88 industrial cases. The end-results were recorded in 126 of the 160 cases from one to nineteen years after the injury. Examination was done in 56 of the 88 industrial cases at the end of a year, and in the remainder, from two to five years after the fracture. The cases were classified as follows: (1) 51 medial and 116 lateral unicondylar fractures; (2) 25 bicondylar Y and V fractures, 16 T fractures and 5 comminuted fractures; (3) 18 fractures of the tibial spine and (4) 9 unusual fractures. The mechanism causing the injury was discussed for each group. In most instances it was a horizontal force acting directly on the condyles. Almost all of the patients were middle-aged. Two were 12 years of age. Treatment in most of the cases consisted of a pillow type of splint which permitted early motion and massage of the knee. Puncture of the joint was done for hemarthrosis. Operation was resorted to in only a few cases of unicondylar fracture with marked dislocation. Direct extension was avoided on account of stretching of articular ligaments. The patients were kept in bed for eight weeks, and longer if there was lateral instability of the knee. Fifty-four per cent of the 160 patients in the hospital showed complete recovery functionally, and 90 per cent were doing their usual work. The industrial cases were influenced by the question of indemnity. Complete recovery was found in only 5 per cent of the patients in this group, and only 29 per cent were doing their usual work.

Immediate Treatment of Compound Fractures.—Orr [43] stressed the advantages of immediate direct fixation of the fragments in compound fractures. The disadvantages and dangers, he believed, were lessened by complete immobilization with dressing by the Orr method. He presented a case illustrating how this method might lead to primary union and reduce the length of the period of disability.

41. von Oettingen, E. N.: Deutsche Ztschr. f. Chir. **241**:471, 1933.

42. Mikkelsen, O.: Acta chir. Scandinav. **73**:1, 1933.

43. Orr, H. W.: The Immediate Treatment of Compound Fractures: The Albee Bone Graft and the Winnett Orr Method of Postoperative Care, J. A. M. A. **101**:1378 (Oct. 28) 1933.

[ED. NOTE.—Primary fixation of compound fractures is desirable, and if the danger of its application can be lessened by this or other methods a considerable advance in the treatment of fractures will have been attained.]

Clinical Study of the Cause of Pseudarthrosis of the Diaphysis of the Long Bones.—Hellstadius [44] made a careful study of 70 cases of pseudarthrosis of the long bones of the extremities. Most of the patients were in Haglund's clinic in Stockholm. The author felt that probably all cases of pseudarthrosis began as a delayed consolidation; in 34 cases there was much callus, and in only 12, no callus. He observed that as pseudarthrosis developed, the periosteal callus smoothed out. Pseudarthrosis developed rarely in children; there were no cases in children under 10. No disease process except syphilis seemed to delay union. In this series only 1 patient, a diabetic subject, was not robust. Glands of internal secretion and vitamins seemed to play a minor rôle in pseudarthrosis, as seen in these cases. Fracture of two bones did not particularly influence the tendency to nonunion. There were 10 cases of pseudarthrosis of the forearm; 5 of both bones, 3 of the radius and 2 of the ulna. There were 29 cases of pseudarthrosis of the bones of the lower part of the leg; 25 of the tibia and 4 of the tibia and fibula. The author concluded that some local predisposition or inhibiting factor led to the pseudarthrosis. This condition was most commonly observed in comminuted fractures where the circulation was poorest. No definite statement could be made as to injury of the nutritive artery, but in 23 of the 70 cases the midpart of the diaphysis was involved. Pseudarthrosis was more common after transverse than after spiral or oblique fractures. In this series there were 31 comminuted, 23 transverse, and 4 oblique fractures. Seven per cent of the cases occurred after compound fractures. In a large series of fractures, pseudarthrosis was found in 2.4 per cent of those operated on and in 0.23 per cent of those reduced manually. In the author's opinion, interposition of the soft parts did not cause nonunion. Nonunion was more common after horn or bone grafts than after the use of Lane plates. Early operation predisposed to nonunion. The best time to perform operation on fractures was during the second week. Violence with laceration and tearing of the soft parts seemed to be the chief predisposing cause. Separation of fragments contributed to nonunion only in that the masses of callus from the ends of the fracture had a longer distance to bridge. Faulty immobilization was of importance as a factor in nonunion only in the later stages when the masses of callus coalesced.

44. Hellstadius, A.: Acta chir. Scandinav. **73**:111, 1933.

PATHOLOGY OF BONE AND JOINT LESIONS

Normal and Pathologic Histology of the Meniscus of the Knee.—
In a concise paper, Tobler [45] discussed his conclusions on a study of
1,000 menisci from cadavers and of 400 operatively removed specimens.
His findings were based on personal observations. Degenerative changes
occurred regularly in normal cartilage after the age of 15. After the
age of 32, all cartilage showed fatty degeneration. Also, degeneration
of bundles of connective tissue fibers was seen regularly after the age
of 37. These changes led to clefts. Ganglions, calcification, ossifica-
tion and acute inflammatory changes in sepsis were reported and illus-
trated. Degenerative changes make the meniscus ready for injury.
The author stated: "Every meniscus which became torn was already
degenerated. The degenerative changes were not the result of injury
as hitherto presupposed, but the cause of it." Reparative changes
occurred in the portion of cartilage not torn free. In operations, there-
fore, Tobler never removed the whole cartilage except in cysts of
the external meniscus) but left the portion attached to the capsule
intact to regenerate new cartilage. He had observed such cartilages a
number of times at reoperation.

[ED. NOTE.—The occurrence of these degenerative changes since
the work of Mandl (not credited by Tobler) are gaining ever-increasing
recognition among those interested in articular pathology.]

*Histologic Changes in the Bone Responsible for the Action of Para-
thyroid Hormone on Calcium Metabolism in Rats.—*In an investigation of
the histologic changes in the bones of rats fed on parathyroid hormone,
Pugsley and Seyle [46] showed that during the period when serum calcium
was increased, i. e., four days, there was marked proliferation of the
osteoclasts. This was taken to be analogous to osteitis fibrosa. There-
after, as the level of the serum calcium returned to normal, osteoblastic
proliferation was seen, and it was suggested that if the administration
of the hormone was continued, "marble bone" would result.

*Resected Knee Joints.—*Ghormley and Brav [47] reviewed the clinical
history, roentgenographic findings, gross and microscopic pathologic
changes and the results of inoculation of guinea-pigs in 236 resections
and 9 amputations of the knee joint. They found that the preoperative
diagnosis was correct in 24.4 per cent of the cases of tuberculosis. The
diagnosis based on microscopic examination of tissue was accurate in
all but 3.2 per cent of the cases.

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45. Tobler, T.: Arch. f. klin. Chir. **177**:482, 1933

46. Pugsley, L. I., and Seyle, H.: J. Physiol. **79**:31, 1933.

47. Ghormley, R. K., and Brav, E. A.: Resected Knee Joint, Arch. Surg. **26**:
465 (March) 1933.

RESEARCH

Effect of Roentgen Rays on Bone Growth and Bone Regeneration.—
Brooks and Hillstrom [48] studied the effect of the roentgen rays on the
growth and regeneration of bone in rabbits. A single 100 per cent skin
erythema dose was given to one tibia, and the animal was killed in from
one to twenty-six days. Marked inhibition of growth was noticed,
which was limited to the exposed bone. Smaller doses of the roentgen
rays, 40 per cent or more of a skin erythema dose, retarded growth
proportionately to the amount given. Very small repeated doses, from
2 to 5 per cent, caused no stimulation or inhibition; 150 per cent of a
skin erythema dose repeated on the following day caused about the
same amount of retardation as a 100 per cent skin erythema dose. A
skin erythema dose of 160 per cent given four times produced less
retardation of growth than 1 skin erythema dose of 100 per cent. Micro-
scopic study of the exposed bones showed serious damage and at times
complete absence of proliferating cartilage. Repair of bone defects was
not inhibited; growth alone was disturbed.

Influence of Periosteum on the Survival of Bone Grafts.—Halde-
man [49] carried out experiments on young rabbits in which he trans-
planted bone from the tibia and the fibula to operative defects in the
radius. He noted the rate of healing of the fracture after the trans-
plantation of (1) fibula with periosteum, (2) grafts of periosteum
alone, (3) osteoperiosteal grafts and (4) grafts consisting of cortex
and of periosteum. It was found that grafts with periosteum favored
the early closure of the defect and the survival of the graft. It was
concluded that the periosteum was the most important part of the graft.

Growth of Epiphyses of the Long Bones in Madder-Fed Pigs.—
From the measurements of the epiphyses of a dozen madder-fed pigs
over a period of five hundred and seven days, Payton [50] concluded that
growth in the length of the epiphyses took place on the side near the
joint, and he found that absorption occurred on the diaphyseal side.
The investigation supported Stevenson's statement that there was an
age sequence of union of the epiphyses, and Humphry's statement that
"the end of the shaft at which the epiphysis is last united is the end at
which growth takes place most quickly."

Experimental Bone Tuberculosis.—According to Mandelstamm,[51]
the localization of tuberculosis in the long bones was not the result pri-
marily of vascular distribution, but the expression of a local immunity
which varies with tissues. The epiphyses showed a greater tendency

48. Brooks, B., and Hillstrom, H. T.: Am. J. Surg. **20**:599 (June) 1933.
49. Haldeman, K. O.: J. Bone & Joint Surg. **15**:302, 1933.
50. Payton, G. C.: J. Anat. **67**:371, 1933.
51. Mandelstamm, M.: Beitr. z. Klin. d. Tuberk. **82**:98, 1933.

to develop tuberculosis than the diaphyseal marrow. In the latter, when tubercles formed in the myeloid tissue, the tendency to regression was marked. Yet when the animal had been previously subjected to a severe attack of fever by injections of typhoid germs the diaphyseal tuberculosis which was produced progressed rapidly. The tubercle did not develop in fatty marrow.

Aseptic Necrosis of the Head of the Femur Following Traumatic Dislocation of the Hip Joint.—Stewart [52] produced aseptic necrosis in young and in adult rabbits by (1) dividing the ligamentum teres femoris and by (2) dividing the ligamentum teres femoris and cutting, in a circular manner, the periosteum of the femoral neck below the head. Division of the ligamentum teres femoris and cutting of the periosteum were only partially successful in producing aseptic necrosis. The ligaments showed a great tendency to reunite, and no marked change occurred when the ligament alone was cut. It was also necessary to interrupt the blood supply of the femoral neck to produce real necrosis of the head.

Manner of Removal of Protein from Normal Joints.—Bauer and his co-workers [53] showed that albumin fractions of protein injected into the normal joints of dogs were readily removed by way of the lymphatic system, and that exercise and massage of the limb hastened this removal. Globulin was removed slowly if at all. The blood stream was an unimportant factor in the removal of protein from a joint.

[ED. NOTE.—These experiments cast new light on the well known fact that massage of the muscles about a joint hastens the removal of a synovial effusion.]

(*To be concluded*)

52. Stewart, W. J.: J. Bone & Joint Surg. **15**:413 (July) 1933.
53. Bauer, W.; Bennett, G. A., and Short, J. A.: J. Exper. Med. **57**:419, 1933.

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